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(54) Title: A USE OF NOVEL 2-OXO-HETEROCYCLIC COMPOUNDS AND THE PHARMACEUTICAL COMPOSITIONS COMPRISING THE SAME

(57) Abstract: The present invention is related to novel use of 2-oxo-heterocyclic compounds having anticancer activity and the process for preparing them and a pharmaceutical composition comprising the same. The present invention provides a pharmaceutical composition for preventing and treating the cancer disease comprising lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer or cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphonas, cancer of the bladder, cancer of the kidney or ureter, or neoplasms of the central nervous system, therefore, it can be used as the therapeutics for treating and preventing cancer diseases.

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A USE OF NOVEL 2-OXO-HETEROCYCLIC COMPOUNDS AND THE PHARMACEUTICAL COMPOSITIONS COMPRISING THE SAME

Technical Field

The present invention relates to novel use of 2-oxo-heterocyclic compounds having anticancer activity and the pharmaceutical compositions comprising the same.

Background Art

Cancer is characterized that cell cluster called as tumor caused by abnormal and uncontrolled cell growth, is formed, permeated into neighboring tissue and severe to be transferred to other organ, which is called as neoplasia. Over than 20 million peoples per year are suffered with cancer in the world and among them 6 million people per year were died from the disease. The origin of cancer is classified into internal factor e.g., genetic factor, immunological factor etc and external factor e.g., various chemical substances, radioactive ray, virus etc. Cancer may occur when the balance between oncogene and tumor suppressor genes is collapsed by above explained factors.

Histone is a nuclear protein bound to nucleus DNA and reversible acetylation reaction of histones occurs at ε-amino group of positively charged lysine tail with reversibility. Since the reaction relates to the formation of highly structure of chromatin, it is reported to be correlated with the regulation of the cell cycle and gene expression accompanied with non-histone proteins.

The balance of acetylated status is sustained with the regulation of two enzyme complexes, histone acetyltransferase (HAT) and histone deacetylase (HDAC), and the change of acetylation level is reported to be essential in the change of gene expression. Therefore, the acetylated state of histone can be regulated by compounds inhibiting HDAC activity, according to the structure, for example, (1) butyrate having short chain fatty acid structure (Newmark et al., *Cancer Lett.* 78, pp1-5, 1994), (2) trichostatin A, suberoylanilide hydroxamic acid (SAHA) and oxamflatin having hydroxamic acid structure (Tsuji et al., *J. Antibiot.* (Tokyo) 29, pp1-6, 1976; Richon et al., *Proc. Natl. Acad. Sci.* USA, 95, pp3003-3007, 1998; Kim et al., *Oncogene* 18, pp2461-2470, 1999), (3) cyclic tetrapeptide structure including the 2-amino-8-oxo-9,10-epoxy-decanoyl (AOE); trapoxin A (Kijima et al., J. Biol. Chem. 268, 22429-22435, 1993), (4) cyclic tetrapeptide structure including the AOE; FR901228 and apicidin (Nakjima et al., *Exp. Cell Res.* 241, pp126-33, 1998; Darkin-Rattray et al., *Proc. Natl. Acad. Sci.* USA, 93, pp13143-13147, 1996), (5) benzamide structure; MS-27-275 (Saito et al., *Proc. Natl. Acad. Sci.* USA, 96, pp4592-4597, 1999).

It has been known that these compounds inhibit HDAC enzyme, induce hyper-acetylation of histone protein, cause to hyper-expression of a specific protein family such as tumor inhibiting factor and inhibit the growth of cancer cell resulting in cancer cell death. Accordingly, the compound inhibiting HDAC selectively can be developed to be a promising candidate drug inhibiting cancer cell and inducing to cell death.

However, there has been not reported or disclosed about novel oxopiperidine compound showing potent inhibiting activity of HDAC activity and anticancer activity in any of above cited literatures, the disclosures of which are incorporated herein by reference.

To investigate novel compound having oxopiperidine skeleton showing potent inhibiting activity of HDAC activity and anticancer activity, the inventors of present invention have intensively carried out *in vitro* experiment concerning the inhibition effect on the HDAC enzyme. As a result of the investigation, the inventors finally completed the present invention by confirming that the novel compound of the present invention inhibited HDAC enzyme and it can be useful as an anti-cancer agent.

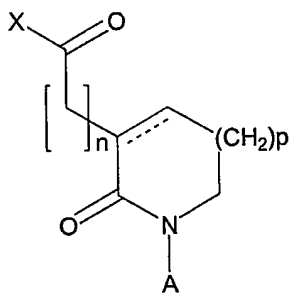
SUMMARY OF THE INVENTION

The present invention also provides a use of novel 2-oxo-heterocyclic compound and the pharmacologically acceptable salt thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases.

The present invention provides a pharmaceutical composition comprising a novel 2-oxo-heterocyclic compound and the pharmacologically acceptable salt thereof as an active ingredient in an effective amount to treat and prevent cancer diseases.

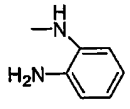
Disclosure of the invention

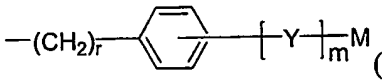
Thus, the present invention provides a novel use of a compound represented by the following general formula (I), and the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(I)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

A is an hydrogen, A1 group or  (A2),

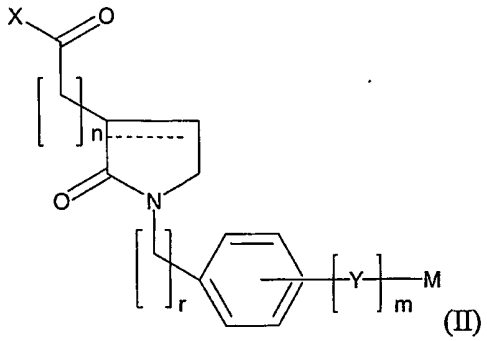
A1 is a lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C5 carbon atoms, a heterocyclic group or aromatic aryl group, preferably, the group selected from thiopenyl group, naphtyl group, pyrrolyl group, furyl group and biphenyl group, wherein Y is a lower alkyl group, lower alkoxy group, nitro, halogen, amine, acetamide, carbonamide or sulfonamide group, M is a lower alkyl group or phenyl group substituted with R', of which R' is a hydrogen, lower alkyl or lower alkoxy group, m and r is independently an integer of 1 to 5 respectively in A2 residue;

p is an integer of 0, 1 or 2;

n is an integer of 1 to 5;

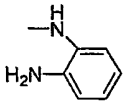
dotted line (⁼) means single bond or double bond.

In preferred embodiment, the present invention also provides a use of the compounds represented by following general formula (II), the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(II)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

Y is a lower alkyl group, lower alkoxy group, nitro, halogen, amine, acetamide, carbonamide or sulfonamide group;

M is a lower alkyl group or phenyl group substituted with R', of which R' is a hydrogen, lower alkyl or lower alkoxy group;

m and r is independently an integer of 1 to 5 respectively;

n is an integer of 1 to 5;

dotted line (⎓) means single bond or double bond.

The preferred compound of general formula (II) is one selected from the group consisting of;

3-[1-(2,4-Dimethoxybenzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxypropionamide,

3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-propionamide,

N-hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(2-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(3-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(4-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(2-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(3-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-[1-(4-bromo-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide,

3-[1-(4-chloro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide,

3-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide,

N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid,

3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid,

N-{4-[3-(2-hydroxycarbamoyl-ethyl)-2-oxo-2,5-dihydro-pyrrole-1-yl-methyl]-phenyl}-benzamide,

N-hydroxy-3-{2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

2-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-acetamide,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)- acetamide,

N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]- acetamide,

2-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide,

2-(1-benzyl-2-oxo-pyrrolidin-3-yl)-N-hydroxy-acetamide,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-pyrrolidin-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-(2-oxo-1-phenethyl-pyrrolidin-3-yl)- acetamide,

3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

3-{1-[2-(3-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

3-{1-[2-(4-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

N-hydroxy-3-{1-[2-(2-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(3-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(4-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

3-{1-[2-(2-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

3-{1-[2-(4-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

N-hydroxy-3-{1-[2-(2-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(3-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(4-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-[2-oxo-1-(2-*p*-tolyl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-[2-oxo-1-(3-*o*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(3-*m*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-{1-[3-(4-isopropyl-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-{1-[3-(4-bromo-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

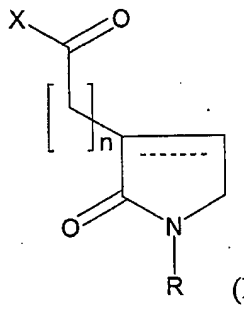
3-{1-[3-(4-chloro-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-{1-[3-(2-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

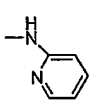
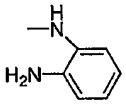
N-hydroxy-3-{1-[3-(3-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide.

In preferred embodiment, the present invention also provides a use of the compounds represented by following general formula (III), the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(III)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

R is a lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C5 carbon atoms, a heterocyclic group or aromatic aryl group, preferably, the group selected from thiopenyl group, naphtyl group, pyrrolyl group, furyl group and biphenyl group;

n is an integer of 1 to 5;

dotted line (┅) means single bond or double bond.

The preferred compound of general formula (III) is one selected from the group consisting of;

N-hydroxy-3-(1-naphthalene-2-ylmethyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide,

N-hydroxy-3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide,

3-(1-allyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-[1-(2-naphthalene-1-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

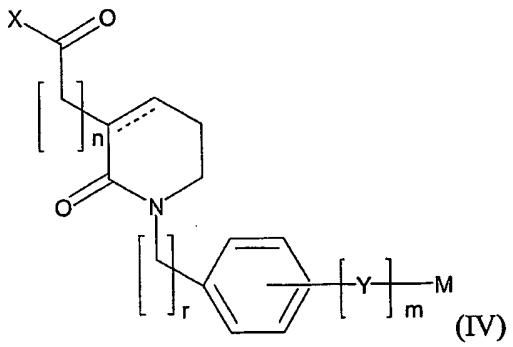
N-hydroxy-3-[1-(2-naphthalene-2-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-[1-(3-biphenyl-4-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

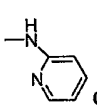
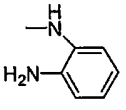
N-hydroxy-3-[1-(3-naphthalene-2-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide.

In preferred embodiment, the present invention also provides a use of the compounds represented by following general formula (IV), the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(IV)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

Y is a lower alkyl group, lower alkoxy group, nitro, halogen, amine, acetamide, carbonamide or sulfonamide group;

M is a lower alkyl group or phenyl group substituted with R', of which R' is a hydrogen, lower alkyl or lower alkoxy group;

m and r is independently an integer of 1 to 5 respectively;

n is an integer of 1 to 5;

dotted line (⎓) means single bond or double bond.

The preferred compound of general formula (IV) is one selected from the group consisting of;

3-[1-(2,4-Dimethoxybenzyl)-2-oxo-1,2,5,6-tetragydropyridin-3-yl]-N-hydroxypropionamide,

N-hydroxy-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy propionamide,

N-hydroxy-3-[2-oxo-1-(4-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

N-hydroxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid,

3-[2-oxo-1-(4-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-pyridin-2-yl-propionamide,

N-(2-amino-phenyl)-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-benzyloxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide,

N-4-[5-(2-hydroxycarbamoyl-ethyl)-6-oxo-3,6-dihydro-2-pyridin-1-yl-methyl]-phenyl-benzamide,

N-hydroxy-3-[1-(4-dimethylsulfonylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

N-hydroxy-3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid,

3-[1-(4-benzoylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid,

3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid,

N-hydroxy-3-(2-oxo-1-phenethyl-piperidine-3-yl)-propionamide,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide,

2-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide,

N-hydroxy-2-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide,

[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid,

(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-N-hydroxy-acetamide,

(2-oxo-1-phenethyl-piperidine-3-yl)-acetic acid,

[2-oxo-1-(3-phenyl-propyl)-piperidine-3-yl]-acetic acid,

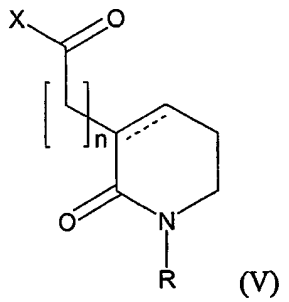
4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-butylamide,

4-(1-phenethyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-butylamide,

N-hydroxy-4-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide,

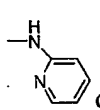
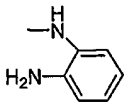
N-hydroxy-4-[2-oxo-1-(3-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide.

In preferred embodiment, the present invention also provides a use of the compounds represented by following general formula (V), the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(V)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

R is a lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C5 carbon atoms, a heterocyclic group or aromatic aryl group, preferably, the group selected from thiophenyl group, naphtyl group, pyrrolyl group, furyl group and biphenyl group;

n is an integer of 1 to 5;

dotted line (⁼) means single bond or double bond.

The preferred compound of general formula (V) is one selected from the group consisting of;

3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

N-Benzyloxy-3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

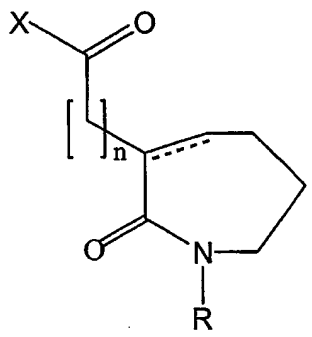
3-(1-Allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-(1-methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-hydroxy-3-(1-(naphthalene-2-yl-methyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

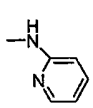
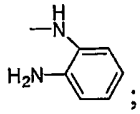
N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide.

In preferred embodiment, the present invention also provides the compounds represented by following general formula (VI), the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases and the use thereof:



(VI)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

R is independently hydrogen atom, lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C4 carbon atoms substituted with a phenyl group which can be substituted with halogen atom or lower alkyl group;

n is an integer of 1 to 5;

dotted line (⎓) means single bond or double bond.

The preferred compound of general formula (VI) is one selected from the group consisting of;

N-3-(1-benzyl-2-oxo-2,5,6,7-tetrahydro-1H-azepin-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-[2-oxo-1-(3-phenyl-ethyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(3-phenyl-butyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide.

It is another object of the present invention to provide the pharmaceutical composition comprising an efficient amount of the compound represented by general formula (I) to (VI) or the pharmaceutically acceptable salt thereof as an active ingredient in amount effective to prevent or treat cancer diseases together with pharmaceutically acceptable carriers or diluents.

The inventive compounds represented by general formula (I) to (VI) can be transformed into their pharmaceutically acceptable salt and solvates by the conventional method well known in the art. For the salts, acid-addition salt thereof formed by a pharmaceutically acceptable free acid thereof is useful and can be prepared by the conventional method. For example, after dissolving the compound in the excess amount of acid solution, the salts are precipitated by the water-miscible organic solvent such as methanol, ethanol, acetone or acetonitrile to prepare acid addition salt thereof and further the mixture of equivalent amount of compound and diluted acid with water or alcohol such as glycol monomethylether, can be heated and subsequently dried by

evaporation or filtrated under reduced pressure to obtain dried salt form thereof.

As a free acid of above-described method, organic acid or inorganic acid can be used. For example, organic acid such as methansulfonic acid, *p*-toluensulfonic acid, acetic acid, trifluoroacetic acid, citric acid, maleic acid, succinic acid, oxalic acid, benzoic acid, lactic acid, glycolic acid, gluconic acid, galacturonic acid, glutamic acid, glutaric acid, glucuronic acid, aspartic acid, ascorbic acid, carbonylic acid, vanillic acid, hydroiodic acid and the like, and inorganic acid such as hydrochloric acid, phosphoric acid, sulfuric acid, nitric acid, tartaric acid and the like can be used herein.

Further, the pharmaceutically acceptable metal salt form of inventive compounds may be prepared by using base. The alkali metal or alkali-earth metal salt thereof can be prepared by the conventional method, for example, after dissolving the compound in the excess amount of alkali metal hydroxide or alkali-earth metal hydroxide solution, the insoluble salts are filtered and remaining filtrate is subjected to evaporation and drying to obtain the metal salt thereof. As a metal salt of the present invention, sodium, potassium or calcium salt are pharmaceutically suitable and the corresponding silver salt can be prepared by reacting alkali metal salt or alkali-earth metal salt with suitable silver salt such as silver nitrate.

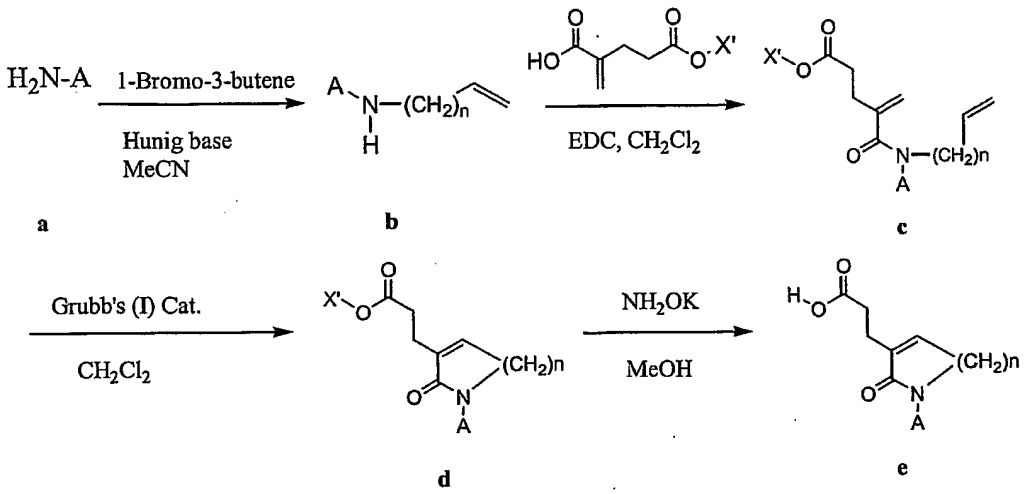
The pharmaceutically acceptable salt of the compound represented by general formula (I) to (VI) comprise all the acidic or basic salt which may be present at the compounds, if it does not indicated specifically herein. For example, the pharmaceutically acceptable salt of the present invention comprise the salt of hydroxyl group such as the sodium, calcium and potassium salt thereof; the salt of amino group such as the hydrogen bromide salt, sulfuric acid salt, hydrogen sulfuric acid salt, phosphate salt, hydrogen phosphate salt, dihydrophosphate salt, acetate salt, succinate salt, citrate salt, tartarate salt, lactate salt, mandelate salt, methanesulfonate(mesylate) salt and *p*-toluenesulfonate (tosylate) salt etc, which can be prepared by the conventional method well known in the art.

There may exist in the form of optically different diastereomers since the compounds represented by general formula (I) to (VI) have unsymmetrical centers, accordingly, the compounds of the present invention comprise all the optically active isomers, R or S stereoisomers and the mixtures thereof. Present invention also comprises all the uses of racemic mixture, more than one optically active isomer or the mixtures thereof as well as all the preparation or isolation method of the diastereomer well known in the art.

The compounds of the invention of formula (I) to (VI) may be chemically synthesized by the methods which will be explained by following reaction schemes hereinafter, which are merely exemplary and in no way limit the invention. The reaction schemes show the steps for preparing the representative compounds of the present invention, and the other compounds also may be produced by following the steps with appropriate modifications of reagents and starting materials, which are envisaged by those skilled in the art.

GENERAL SYNTHETIC PROCEDURES

Scheme 1



a **b** **c** **d** **e**

As depicted in above Scheme **1**, the scheme explains the process for preparing hydroxamine compound (**e**) consisting of 4 steps;

At 1st step, compound (**a**) is reacted with 1-bromo-3-butene under organic solvent in the presence of Hung base to synthesize compound (**b**). In the step, an organic solvent such as acetonitrile, dichloromethane etc are preferable and diethylisopropylamine can be used as a Hung base in the amount of 2 to 3 equivalents to the compound (**a**). It is preferable the reaction is performed at the temperature ranging from 0℃ to R. T.

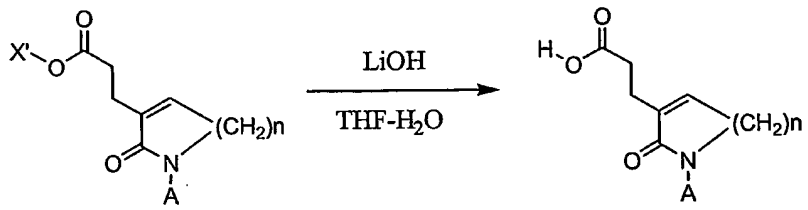
At 2nd step, the compound (**b**) obtained in step 1 is reacted with mono acid in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide(EDC) under an organic solvent to synthesize the compound (**c**). In the step, an organic solvent such as methylenechloride, THF etc are preferable and a mono acid such as 2-methylene-pentandionic acis-5-methyl ester in the amount of 1 to 1.2 equivalents to the compound (**b**) is preferable. It is preferable the reaction is performed at the temperature ranging from 0℃ to R. T.

At 3rd step, the compound (**c**) obtained in step 2 is converted into the compound (**d**) in the presence of Grubb's (I) catalyst such as Ruthenium catalyst under organic solvent. In the step, it is preferable to use the catalyst in the amount of 0.02 to 0.1 equivalents to the compound (**c**) at the temperature ranging from 0℃ to R. T.

At 4th step, the compound (**d**) obtained in step 3 is reacted with amine salt to synthesize hydroxamide compound (**e**) in case that X is NHOH in general formula I

compounds. In the step, it is preferable to use potassium hydroxamide ($KONH_2$) in the amount of 2 to 3 equivalents to the compound (**d**) at the temperature ranging from 0℃ to R. T.

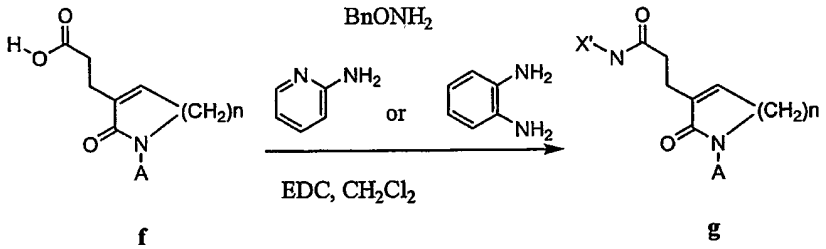
Scheme 2



d **f**

As depicted in the above Scheme 2, the ester compounds (**d**) is reacted with hydroxide metal salt under the organic solvent such as THF to synthesize the carboxylic acid (**f**). In the reaction, it is preferable to use LiOH in the amount of 2 to 3 equivalents to the compound (**d**) at the temperature ranging from 0℃ to R. T.

Scheme 3

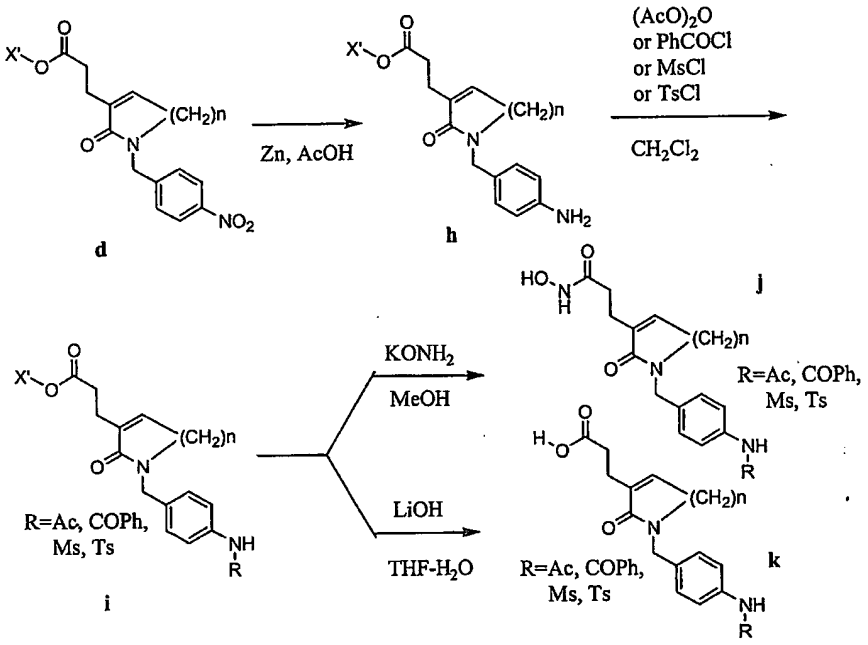


f **g**

As depicted in the above Scheme 3, the carboxylic acid compound (**f**) obtained in Scheme 2 is reacted with benzyloxyamine($BnONH_2$), pyridylamine or diaminobenzene in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) under organic solvent to synthesize the amide compounds of which X is benzyloxyamine($BnONH_2$), pyridylamine or diaminobenzene group. In the reaction, it is preferable to use benzyloxyamine($BnONH_2$), pyridylamine or diaminobenzene in the amount of 1 to 1.5 equivalents to the compound (**f**) at the temperature ranging

from 0℃ to R. T.

Scheme 4



As shown in the above Scheme 4, the amide compound (**j**) and carboxylic acid compound (**k**) are prepared by following procedure from the ester compounds (**d**):

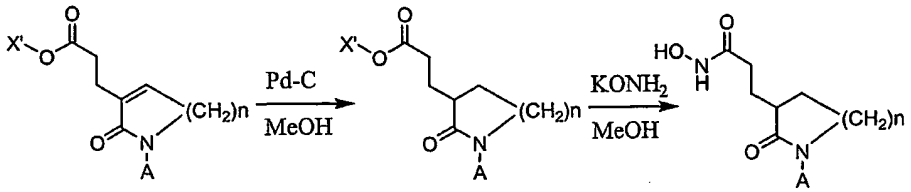
At 1st step, the compound (**d**) prepared from Scheme 2 is reacted with zinc under organic solvent to synthesize the compound (**h**). In the step, it is preferable to use the zinc in the amount of 2 to 5 equivalents of the compound (**h**).

At 2nd step, the compound (**h**) obtained in step 1 is reacted with $(AcO)_2O$, PhCOCl, MsCl or TsCL to synthesize the compound (**i**). In the reaction, it is preferable to use $(AcO)_2O$, PhCOCl, MsCl or TsCL in the amount of 1 to 3 equivalents to the compound (**h**).

At 3rd step, the compound (**i**) obtained in step 2 is reacted with amine salt under the organic solvent such as methanol to produce the hydroxamide compound (**j**), i.e., the general formula I compound wherein X is NHOH where the amine salt is preferably used in the amount of 2 to 3 equivalents to the compound (**i**), or with hydroxide metal salt such as LiOH under the organic solvent such as THF to produce the carboxylic acid compound (**k**), i.e., the general formula I compound wherein X is OH where the metal salt is preferably used in the amount of 2 to 3 equivalents to the

compound (i).

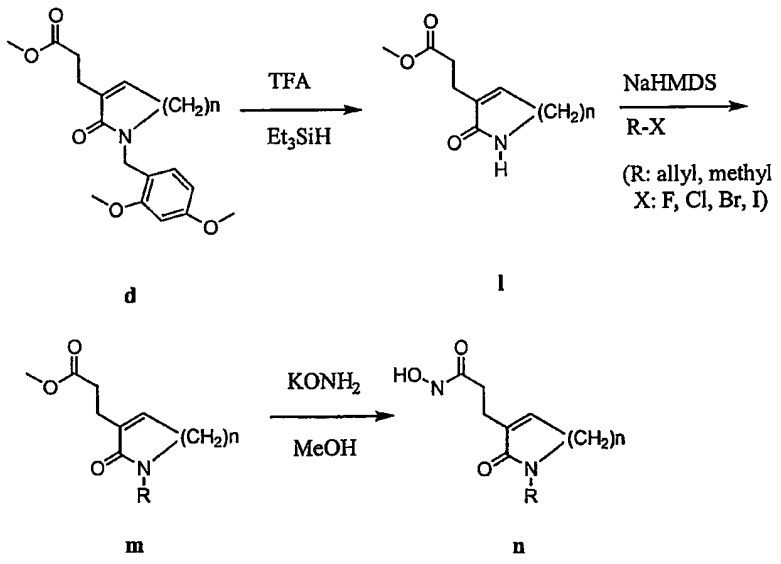
Scheme 5



d **l** **m**

As shown in Scheme 5, the 1,2,5,6-dihydropyridine compound **(d)** is reduced to the piperidine compound **(l)** by reacting with palladium-carbon (Pd/C) under alcohol solvent in the amount of 0.1 to 0.2 equivalents of compound **(d)** and further the piperidine compound **(l)** is reacted with $KONH_2$ under MeOH to synthesize the compound **(m)**. In the reaction, it is preferable to use the amine salt in the amount of 2 to 3 equivalents to the compound **(m)** at the temperature ranging from 0℃ to R. T.

Scheme 6

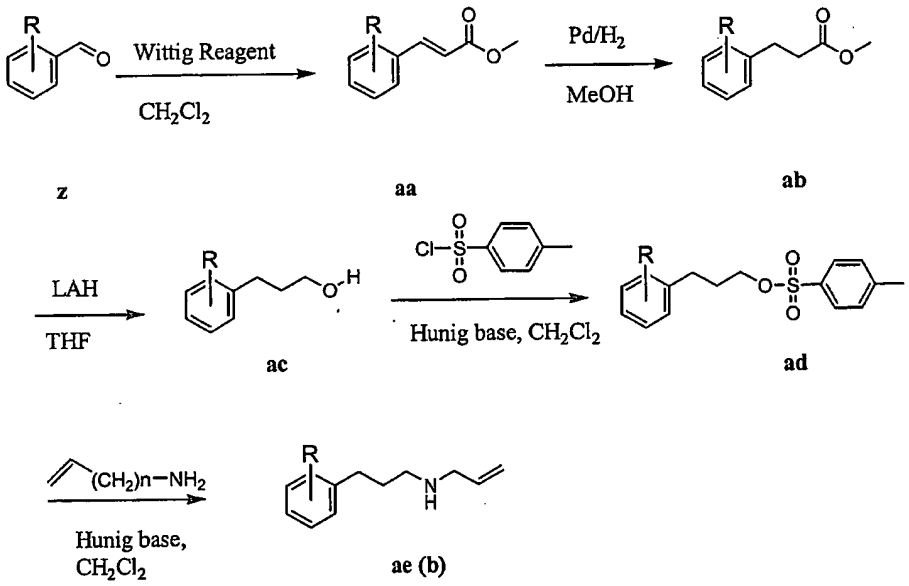


d **l**

m **n**

As shown in Scheme 6, the benzyl compound **(d)** is reacted with triethysilane(TES) in the amount of 1 to 1.5 equivalent of the compound (d) under TFA solution to produce the compound **(l)**. The compound **(l)** is further reacted with hexamethyldisilylazidesodium (NaHMDS) under THF solvent and subsequently reacted with R-X (R: ally, methyl etc, X: halogen atom) to produce the compound **(m)**. In the reaction, it is preferable to use the NaHMDS in the amount of 1 to 1.5 equivalents to the compound **(l)**.

Scheme 7



As shown in Scheme 7, the compound **(b)** as a starting material is prepared by following procedure: At 1st step, the compound **(z)** which can be procure by conventional market or chemical company is reacted with Wittig reagent under the organic solvent such as dichloromethane to synthesize to the compound **(aa)**. In the step, it is preferable to use the Wittig reagent in the amount of 1.5 to 2 equivalents of the compound **(z)** at the temperature ranging from 60 to 70℃.

At 2nd step, the compound **(aa)** obtained in step 1 is reacted with Pd/C in the amount of 0.1 to 0.2 equivalents of the compound **(aa)** under ethyl alcohol solvent to synthesize the compound **(ab)**.

At 3rd step, the compound (**ab**) obtained in step 2 is reacted with lithium aluminum hydride (LAH) under the organic solvent such as THF to produce the compound (**ac**) at 0 ℃.

At 4th step, the compound (**ac**) substiteis reacted with p-toluenesulfonylchloride, diisopropylethylamine or 4-(dimethylamino) pyridine in the amount of 0.1 to 0.2 equivalents of the compound (**aa**) under ethyl alcohol solvent to synthesize the compound (**ab**).

At 5th step, both of allyl amine and Hunig base, i.e., diisopropylethylamine are added to the compound (**ad**) dissolved in acetonitrile, mixed and stirred for six hours at 80 ℃ to produce the compound (**ae**), one of the compound (**b**).

The present invention also provides a pharmaceutical composition comprising an efficient amount of the compound represented by general formula (I) to (VI) or the pharmaceutically acceptable salt thereof as an active ingredient in amount effective to treat or prevent cancer diseases together with pharmaceutically acceptable carriers or diluents.

The compound of formula (I) to (VI) according to the present invention can be provided as a pharmaceutical composition containing pharmaceutically acceptable carriers, adjuvants or diluents. For example, the compounds of the present invention can be dissolved in oils, propylene glycol or other solvents which are commonly used to produce an injection. Suitable examples of the carriers include physiological saline, polyethylene glycol, ethanol, vegetable oils, isopropyl myristate, etc., but are not limited to them. For topical administration, the compounds of the present invention can be formulated in the form of ointments and creams.

The pharmaceutical compositions comprising the compound of the present invention can be treat and prevent the cancer disease, for example, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer or cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (eg., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphonas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), or neoplasms

of the central nervous system (e.g., primary CNS lymphoma, spinal axis tumors, brain stem gliomas or pituitary adenomas).

The compound of the present invention has potent anti-cancer activity, and the pharmaceutical composition of the present invention thus may be employed to treat or prevent the cancer disease.

The present invention also provides a method of preventing or treating the cancer disease which comprises administering compound selected from the group consisting of compounds of formula (I) to (VI) or pharmaceutical acceptable salts thereof in need of such prevention or treatment a therapeutically effective amount of the salt or a pharmaceutically acceptable hydrate thereof as an anti-cancer agent.

Hereinafter, the following formulation methods and excipients are merely exemplary and in no way limit the invention.

The compounds of the present invention in pharmaceutical dosage forms may be used in the form of their pharmaceutically acceptable salts, and also may be used alone or in appropriate association, as well as in combination with other pharmaceutically active compounds.

The compounds of the present invention may be formulated into preparations for injections by dissolving, suspending, or emulsifying them in aqueous solvents such as normal saline, 5% Dextrose, or non-aqueous solvent such as vegetable oil, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol. The formulation may include conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives.

The desirable dose of the inventive compounds varies depending on the condition and the weight of the subject, severity, drug form, route and period of administration, and may be chosen by those skilled in the art. However, in order to obtain desirable effects, it is generally recommended to administer at the amount ranging 0.0001 - 100 mg/kg, preferably 0.001 – 100 mg/kg by weight/day of the inventive compounds of the present invention. The dose may be administered in single or divided into several times per day. In terms of composition, the compounds should be present between 0.0001 to 10% by weight, preferably 0.0001 to 1% by weight based on the total weight of the composition.

The pharmaceutical composition of present invention can be administered to a subject animal such as mammals (rat, mouse, domestic animals or human) via various routes. All modes of administration are contemplated, for example, administration can be made orally, rectally or by intravenous, intramuscular, subcutaneous, intrathecal, epidural or intracerebroventricular injection.

The present invention is more specifically explained by the following examples. However, it should be understood that the present invention is not limited to these examples in any manner.

BEST MODE FOR CARRING OUT THE INVENTION

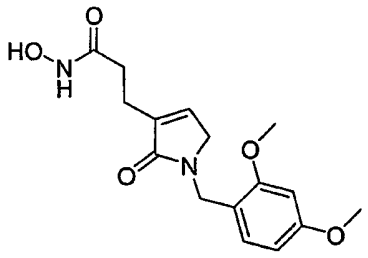
It will be apparent to those skilled in the art that various modifications and variations can be made in the compositions, use and preparations of the present invention without departing from the spirit or scope of the invention.

The present invention is more specifically explained by the following examples. However, it should be understood that the present invention is not limited to these examples in any manner.

EXAMPLES

The following Reference Example, Examples and Experimental Examples are intended to further illustrate the present invention without limiting its scope.

Example 1. Preparation of 3-[1-(2,4-Dimethoxybenzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxypropionamide(1e)



Step 1. Preparation of allyl-(2,4-dimethoxybenzyl)amine (1b)

0.32ml of allylbromide (3.66mM) and 0.7 ml of diisopropyl ethylamine (3.99 mM) were added to the reaction solution containing 500mg of 2, 4-

dimethoxybenzylamine (3.33 mM) dissolved in methylene chloride with stirring and the solution was left alone at room temperature. After the reaction mixture was neutralized with 10% NaOH solution, the mixture was extracted with chloroform, washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 276 mg of allyl-(2,4-dimethoxybenzyl)amine (1b) (yield : 40%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J= 8.1 Hz, 1H), 6.44-6.39 (m, 2H), 5.99-5.86 (m, 1H), 5.21-5.09 (m, 2H), 3.79 (d, J= 6.0 Hz, 6H), 3.74 (s, 2H), 3.23 (d, J= 6.0 Hz, 2H)

Step 2. Preparation of 4-[allyl-(2,4-dimethoxy-benzyl)-carbamoyl]-pent-4-enoic acid methyl ester (1c)

253 mg of 2-methylene-pentane dionate-5-methyl ester (1.6 mM), 331mg of [3-(dimethylamino)propyl]-3-ethylcarbodiimide (1.73 mM) and 48mg of 4-(dimethylamino)pyridine (0.39 mM) were added to 0.5 M of reaction solution dissolving the compound (1b) prepared by above step 1 in methylene chloride and the mixture was stirred for 10 hrs at room temperature. After the resulting mixture was washed with 5% HCl solution (10 ml), the mixture was extracted with ethylacetate, washed with saturated NaCl. And then the extracts were washed with saturated 10ml of $NaHCO_3$ solution and NaCl solution to separate into an organic layer and water layer. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:2) as an eluant to give 324 mg of 4-[allyl-(2,4-dimethoxy-benzyl)-carbamoyl]-pent-4-enoic acid methyl ester (1c) (yield : 70%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.44 (d, 2H), 5.72 (s, 1H), 5.12 (s, 4H), 4.56-4.81 (m 2H), 3.91-3.83 (m, 2H), 3.78 (d, J= 5.3 Hz, 6H), 3.65 (d, J= 1.4 Hz, 3H), 2.63 (t, J= 5.7 Hz, 2H), 2.54 (t, J= 5.4 Hz, 2H)

Step 3. Preparation of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (1d)

324mg of the compound (1c) (0.933 mM) prepared by the above Step 2 was added to the catalyst solution containing 74mg of ruthenium (0.09 mM) dissolved in 93ml of CH_2Cl_2. Then the mixture was stirred for 24 hrs at room temperature, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column

chromatography with a solvent mixture mixed with EtOAc and hexanes (1:1) as an eluant to give 268 mg of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-2,5-dihydro-1H-pyrole-3-yl]-propionic acid methyl ester (1d) (yield : 90%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J= 9.0 Hz, 1H), 6.61(br t, 1H), 6.43(s, 1H), 6.40 (d, J= 2.7 Hz, 1H), 4.56 (s, 2H), 3.78(d, J= 5.4 Hz, 9H), 3.65(s, 2H), 2.61(s, 4H)

Step 4. Preparation of 3-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (1e)

100mg of compound (d) prepared by the above Step 3 was dissolved in methanol solution (0.313 mM) and then 1.7 M methanolic suspension solution containing NH_2OK (0.27 ml, 0.47 mM) was added thereto at 0°C and the resulting mixture was stirred for 4 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 50 mg of 3-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (1e) (yield : 50%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.04 (d, J= 8.1 Hz,1H), 6.83 (s, 1H), 6.53-6.44 (m, 2H), 4.54(s, 2H), 3.81 (t, J= 2.0 Hz, 6H), 2.56 (t, J= 7.2 Hz, 2H), 2.34 (t, J= 7.4 Hz, 2H), 1.9 (s, 3H)

Example 2. Preparation of 3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide (2e)

3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide (2e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 3. Preparation of N-hydroxy-3-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (3e)

N-hydroxy-3-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (3e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 4. Preparation of N-hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (4e)

N-hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (4e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 5. Preparation of N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (5e)

N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (5e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 6. Preparation of N-hydroxy-3-[1-(2-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (6e)

N-hydroxy-3-[1-(2-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (6e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 7. Preparation of N-hydroxy-3-[1-(3-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (7e)

N-hydroxy-3-[1-(3-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (7e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 8. Preparation of N-hydroxy-3-[1-(4-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (8e)

N-hydroxy-3-[1-(4-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (8e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 9. Preparation of N-hydroxy-3-[1-(2-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (9e)

N-hydroxy-3-[1-(2-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (9e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 10. Preparation of N-hydroxy-3-[1-(3-methoxy-benzyl)-2-oxo-2,5-

dihydro-1H-pyrrol-3-yl]-propionamide (10e)

N-hydroxy-3-[1-(3-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (10e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 11. Preparation of N-hydroxy-3-[1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (11e)

N-hydroxy-3-[1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (11e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 12. Preparation of 3-[1-(4-bromo-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide (12e)

3-[1-(4-bromo-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (12e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

Example 13. Preparation of 3-[1-(4-chloro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide (13e)

3-[1-(4-chloro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (13e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

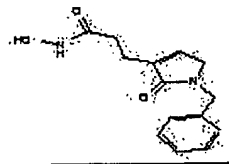
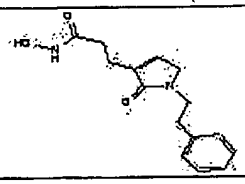
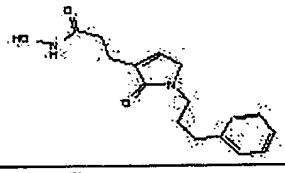
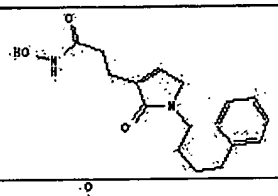
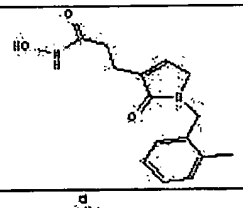
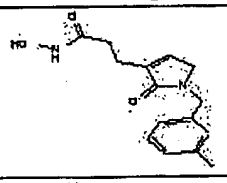
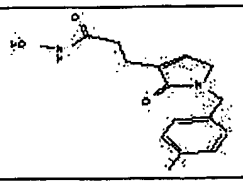
Example 14. Preparation of 3-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide (14e)

3-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide (14e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

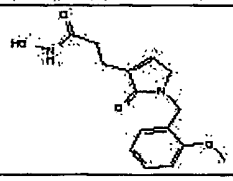
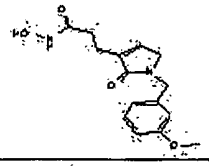
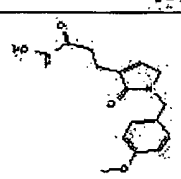
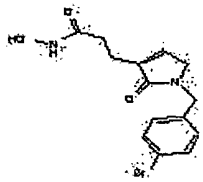
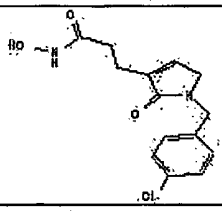
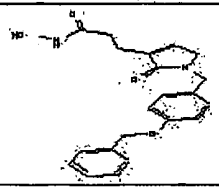
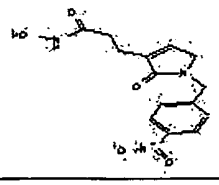
Example 15. Preparation of N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (15e)

N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (15e) was prepared by the similar procedure described in above Example 1 (*See* Table 1).

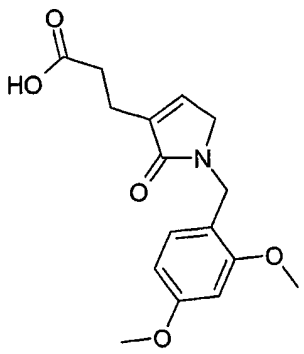
[Table 1a]

Example	Chemical structure	NMR spectrum
2		7.30-7.14 (m, 5H), 6.71 (d, J= 18.3 Hz, 1H), 4.59 (d, J= 7.8 Hz, 2H), 3.73 (s, 2H), 2.63 (s 4H).
3		7.25-7.09 (m ,5H), 6.64 (s, 1H), 3.62 (t, J = 6.1 Hz, 4H), 2.81 (t, J= 7.3 Hz, 2H), 2.52 (s, 2H), 2.30 (d, J= 6.6 Hz, 2H)
4		7.21 (d, J= 7.5 Hz, 2H), 7.12(d, J= 6.6 Hz, 3H), 6.72 (s, 1H), 3.75 (s, 2H), 3.41 (s, 2H), 2.57 (d, J= 6.3 Hz, 6H), 2.44 (s, 1H), 1.82 (s, 2H)
5		7.28-7.12 (m, 5H), 6.73 (s, 1H), 3.78 (d, J= 9.0 Hz, 2H), 3.43 (s, 2H), 2.61 (s, 5H), 1.58 (s, 5H)
6		7.12 (s, 5H), 6.67 (s, 1H), 4.58 (d, J= 8.4 Hz, 2H), 3.64 (s, 2H), 2.61 (s, 4H), 2.34-2.22 (m, 3H)
7		7.15 (d, J= 6.9 Hz, 1H), 7.02-6.95 (m, 3H), 6.74 (s, 1H), 4.52 (d, J= 8.4 Hz, 2H), 3.70 (s, 2H), 2.60 (s, 3H), 2.27 (d, J= 4.8 Hz, 4H)
8		7.09-7.03 (m, 4H), 6.70 (d, J= 18.3 Hz, 1H), 4.54 (d, J= 7.2 Hz, 2H), 3.70 (s, 2H), 2.61 (s, 3H), 2.45 (s, 1H), 2.28 (d, J= 13.5 Hz, 3H)

[Table 1b]

Example	Chemical structure	NMR spectrum or LC-MS data
9		7.23-7.18 (m, 1H), 7.08 (d, *J*= 3.5 Hz, 1H), 6.84 (dd, *J*= 5.8 Hz, 2H), 6.72 (s, 1H), 4.59 (s, 2H), 3.78 (s, 3H), 3.75 (s, 2H), 2.60 (s, 2H), 2.44 (s, 2H)
10		7.16 (t, *J*= 4.8 Hz, 1H), 6.73 (t, *J*= 5.4 Hz, 3H), 6.68 (s, 1H), 4.53 (d, *J*= 10.5 Hz, 2H), 3.72 (t, *J*= 5.2 Hz, 5H), 2.59 (s, 2H), 2.43 (s, 2H)
11		7.06-7.014 (m, 4H), 6.71 (s, 1H), 4.49 (s, 2H), 3.66 (s, 2H), 2.59 (s, 2H), 2.43 (s, 2H), 2.25 (s, 3H)
12		7.40 (d, *J*= 7.8 Hz, 2H), 7.05 (d, *J*= 8.4 Hz, 2H), 6.78 (s, 1H), 4.53 (s, 2H), 4.39 (s, 2H), 3.76 (s, 2H), 2.57 (t, *J*= 5.7 Hz, 2H), 2.31 (t, *J*= 7.2 Hz, 2H)
13		7.28-7.07 (m, 2H), 6.95 (t, *J*= 8.2 Hz, 2H), 6.74 (s, 1H), 4.52 (s, 2H), 3.60 (s, 2H), 2.54 (s, 2H), 2.31 (d, *J*= 7.2 Hz, 2H)
14		7.41-7.30 (m,5H), 7.14 (d, *J*= 8.4 Hz, 2H), 6.91 (d, *J*= 8.4 Hz, 2H), 6.67 (s, 1H), 5.02 (s, 2H), 4.55 (s, 2H), 3.72 (s, 2H), 2.65 (2, 4H)
15		RT : 3.82-4.54 (Mass : 306.1)

Example 16. Preparation of 3-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid (16f)



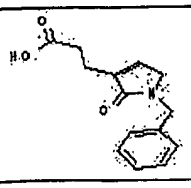
10.8mg of $LiOH \cdot H_2O$ solution (0.25 mM) was added to 0.86ml of THF solution containing 55mg of 3-[1-(2,4-dimethoxy benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (0.17 mM) in a dropwise manner at 0°C. The reaction mixture was stirred for 2hrs at 0°C adjust pH 1 with 5% HCl was added to the mixture to pH 1. Then the mixture was extracted three times with 10ml of ethyl acetate, the organic layer was washed with 15ml of saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 41 mg of 3-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid (16f) (yield : 80%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J= 9.0 Hz, 1H), 6.65 (br t, 1H), 6.41 (ab,J= 6.5 Hz,1.1 Hz, 2H), 4.57 (s, 2H), 3.81-3.76 (m, 8H), 2.63 (s, 4H)

Example 17. Preparation of 3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid (17f)

3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid (17f) was prepared by the similar procedure described in above Example 16 (*See* Table 2).

[Table 2]

Example	Chemical structure	NMR spectrum data
17		7.33-7.19 (m, 5H), 6.69 (br t, 1H), 4.62 (s, 2H), 3.74 (s, 2H), 2.66 (s, 4H)

Example 18. Preparation of N-{4-[3-(2-hydroxycarbamoyl-ethyl)-2-oxo-2,5-dihydro-pyrrole-1-yl-methyl]-phenyl}-benzamide (18j)

Step 1. Preparation of 3-[1-(4-amino-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (h)

90mg of 3-[1-(4-nitro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (0.3 mM) was dissolved in methanol solution at room temperature. And then 290mg of Zn (4.44mM) and 0.02ml of acetic acid (0.3 mM) were added thereto and the mixture was stirred for 48 hrs at room temperature. The resulting compound was purified by Silica gel column chromatography with ethylacetate as an eluant to give 20 mg of 3-[1-(4-amino-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (h) (yield : 25%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.01 (d, J= 8.4 Hz, 2H), 6.62 (d, J= 1.8Hz, 2H), 6.60 (br t, 1H) 4.48 (s, 2H), 3.68 (d, J= 1.2 Hz, 3H), 3.65 (s, 4H), 2.66-2.58 (m, 4H)

Step 2. Preparation of 3-[1-(4-benzoylamino-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (i)

10mg of 3-[1-(4-amino-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (h) prepared by above Step 1 was dissolved in methylene chloride solution (0.04mM) at room temperature. And then 8.5 μl of benzoyl chloride (0.07 mM) and 19.1 μl of diisopropylamine (0.11mM) were added thereto and the mixture was stirred for 2 hrs at 0°C. The reaction was stopped by adding methanol and the mixture was extracted three times with 10ml of ethyl acetate. The organic layer was washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with a solvent mixture mixed with ethyl acetate and hexane (1:2) as an eluant to give 12 mg of 3-[1-(4-benzoylamino-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (i) (yield : 87%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.88-7.83 (m, 3H), 7.62-7.47 (m, 6H), 6.68 (br t, 1H), 4.62 (S, 2H), 3.75 (d, 2H), 3.68 (s, 3H), 2.67-2.64 (m, 4H)

Step 3. Preparation of N-{4-[3-(2-hydroxycarbamoyl-ethyl)-2-oxo-2,5-dihydro-pyrrole-1-yl-methyl]-phenyl}-benzamide (j)

7mg of compound (i) prepared by the above Step 2 was dissolved in methanol solution (0.02 mM) and then 1.7 M methanolic suspension solution containing NH_2OK

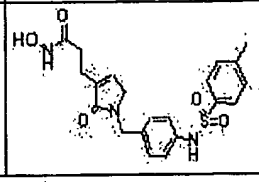
(0.4 ml, 0.68 mM) was added thereto at 0°C and the resulting mixture was stirred for 8 hrs at room temperature. The resulting mixture was neutralized with 0.01 ml of acetic acid, diluted with 10% methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 3.2 mg of N-{4-[3-(2-hydroxycarbamoyl-ethyl)-2-oxo-2,5-dihydro-pyrrole-1-yl-methyl]-phenyl}-benzamide (j) (yield : 46%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J= 6.6 Hz, 2H), 7.62 (d, J= 8.7 Hz, 2H), 7.53-7.39 (m, 4H), 7.17(d, J= 8.4 Hz, 2H), 6.77 (br t, 1H), 4.57 (s, 2H), 3.77 (s, 2H), 2.58 (t, J= 7.3 Hz, 2H), 2.31 (t, J= 7.2Hz, 2H)

Example 19. Preparation of N-hydroxy-3-{2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (19j)

N-hydroxy-3-{2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (19j) was prepared by the similar procedure described in above Example 18 (*See* Table 3).

[Table 3]

Example	Chemical structure	NMR spectrum data
19		7.61 (t, J= 7.0 Hz, 3H), 7.05-6.89 (m, 6H), 4.54 (s, 3H), 3.74 (s, 3H), 3.39 (s, 3H), 2.37 (s, 3H), RT : 3.87-4.34 (Mass : 430.0)

Example 20. Preparation of 2-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-acetamide(20q)

Step 1. Preparation of 3-(allyl-benzyl-carbamoyl)-but-3-enoic acid methyl ester (o)

587mg of 2-methylene-succinate 4-methyl ester (4.07mM), 781mg of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (4.07mM) and 75mg of 4-(dimethylamino)pyridine (0.61mM) were added to the reaction solution containing 300mg of allylbenzylamine (2.04 mM) dissolved in methylene chloride solution (0.5M) with stirring for 10 hrs at room temperature. After the resulting mixture was washed with 5% HCl solution (10 ml), the mixture was diluted with ethyl acetate, washed with

10ml of solution mixture mixed with saturated $NaHCO_3$ solution and saturated NaCl solution to separate into an organic layer and water layer. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:1) as an eluant to give 272 mg of 3-(allyl-benzyl-carbamoyl)-but-3-enoic acid methyl ester (o) (yield : 49%).

^{1}H-NMR (300 MHz, CDCl3) δ 7.30-7.22 (m, 5H), 5.84-5.71 (m, 1H), 5.37-5.15 (m, 4H), 4.75-4.65 (m, 2H), 4.02 (s, 2H), 3.63 (s, 3H), 3.48 (s, 2H)

Step 2. Preparation of (1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-acetic acid methyl ester (p)

234mg of 3-(allyl-benzyl-carbamoyl)-but-3-enoic acid methyl ester (o) (0.1mM) prepared by the above Step 1 was added to the catalyst solution containing 36mg of Grubb's (I) catalyst (0.04mM) such as ruthenium dissolved in CH_2Cl_2 under Ar atmosphere. Then the mixture was stirred for 24 hrs at room temperature, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:2) as an eluant to give 180 mg of (1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-acetic acid methyl ester (p) (yield : 85%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.33-7.18 (m, 5H), 6.94 (t, J= 1.5 Hz, 1H), 4.61 (s, 2H), 3.79(d, J= 0.7 Hz, 2H), 3.70 (s, 3H), 3.37 (d, J= 1.5 Hz, 2H)

Step 3. Preparation of 2-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-acetamide (q)

24mg of (1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-acetic acid methyl ester (p) prepared by the above Step 2 was dissolved in methanol solution (0.1 mM) and then 1.7 M methanolic suspension solution containing NH_2OK (0.4 ml, 0.68 mM) was added thereto at 0°C and the resulting mixture was stirred for 4 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10% methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 12 mg of 2-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-acetamide (q) (yield : 48%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35-7.21 (m, 5H), 7.05 (br t, 1H), 4.63 (s, 2H), 3.90 (s, 2H), 3.30 (t, J= 1.5 Hz, 1H), 3.13 (s, 2H)

Example 21. Preparation of 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide (21q)

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide (21q) was prepared by the similar procedure described in above Example 20 (*See* Table 4).

Example 22. Preparation of N-hydroxy-2-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)- acetamide (22q)

N-hydroxy-2-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-acetamide (22q) was prepared by the similar procedure described in above Example 20 (*See* Table 4).

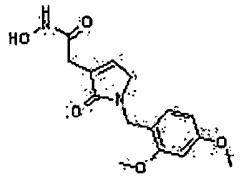
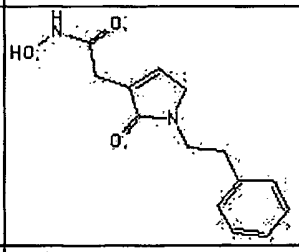
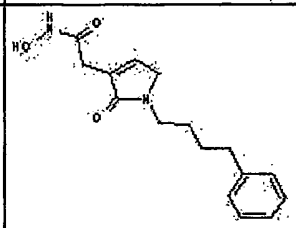
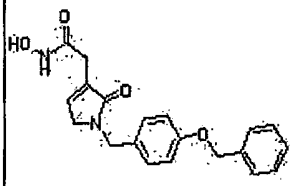
Example 23. Preparation of N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]- acetamide (23q)

N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]-acetamide (23q) was prepared by the similar procedure described in above Example 20 (*See* Table 4).

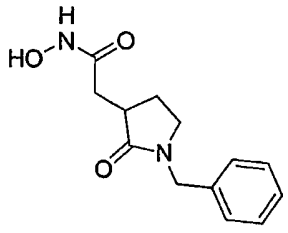
Example 24. Preparation of 2-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide (24q)

2-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide (24q) was prepared by the similar procedure described in above Example 20 (*See* Table 4).

[Table 4]

Example	Chemical structure	NMR spectrum data
21		7.12 (d, J= 8.4 Hz, 2H), 6.90(d, J= 20.7 Hz, 1H), 6.43 (d, J= 6.0 Hz), 4.57 (d, J= 2.7 Hz, 2H), 3.86 (d, J= 15.9 Hz, 2H), 3.79 (d, J= 3.0 Hz, 6H)
22		7.29-7.14 (m, 5H), 6.90 (br t, 1H), 3.75-3.65 (m, 4H), 3.23 (s, 1H), 2.92-2.84 (m, 2H)
23		7.21 (t, J= 7.4 Hz, 2H), 7.11 (d, J= 7.8 Hz,3H), 6.76 (br t, 1H), 5.22 (s, 1H), 3.30 (t, J= 3.3 Hz, 1H), 2.58 (t, J= 7.0 Hz, 2H), 2.04 (s, 3H), 1.82 (s, 3H), 1.57 (s, 4H)
24		7.39-7.31 (m, 5H), 7.13 (d, J= 8.4 Hz, 2H), 6.92 (d, J= 8.7 Hz, 3H), 5.03 (s, 2H), 4.56 (s, 2H), 3.82 (d, J= 13.8 Hz, 2H), 3.53 (s, 1H), 3.31 (s, 1H)

Example 25. Preparation of 2-(1-benzyl-2-oxo-pyrrolidin-3-yl)-N-hydroxy-acetamide (25s)



Step 1. Preparation of (2-oxo-1-phenethyl-pyrrolidin-3-yl)-acetic acid methyl ester (25r)

30mg of (1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-acetic acid methyl ester

was dissolved in methanol solution (0.12 mM) under nitrogen atmosphere. Then 2.6mg of Pd-C (0.02mM) was added thereto, and hydrogenated under a hydrogen balloon for 1 to 2 hrs at room temperature. The reaction mixture was filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with with a solvent mixture mixed with EtOAc and hexane (1:1) as an eluant to give (2-oxo-1-phenethyl-pyrrolidin-3-yl)-acetic acid methyl ester (25r) (yield : 95%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34-7.19 (m, 5H), 4.44 (ab, J= 19.8 Hz, 7. 4Hz, 2H), 3.67 (s, 3H), 3.21-3.16 (m, 2H), 2.9 6(m, 2H), 2.43 (dd, J= 8.7 Hz, 7.9 Hz, 1H), 2.34-2.23 (m, 1H), 1.76-1.65 (m, 1H)

Step 2. Preparation of 2-(1-benzyl-2-oxo-pyrrolidin-3-yl)-N-hydroxy-acetamide (25s)

12mg of (2-oxo-1-phenethyl-pyrrolidin-3-yl)-acetic acid methyl ester (25r) prepared by the above Step 1 was dissolved in methanol solution (0.04 mM) and then 1.7 M methanolic suspension solution containing NH_2OK (0.07 ml, 0.12 mM) was added thereto at 0°C and the resulting mixture was stirred for 4 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10% methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 1.6 mg of 2-(1-benzyl-2-oxo-pyrrolidin-3-yl)-N-hydroxy-acetamide (25s) (yield : 8%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34-7.19 (m, 5H), 4.46 (d, J= 8.1Hz, 2H), 3.35-3.20 (m, 2H), 3.01-2.71 (m, 2H), 2.66-2.44 (m, 2H), 2.35-2.22 (m, 2H), 1.81-1.58 (m, 2H)

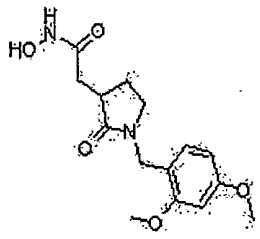
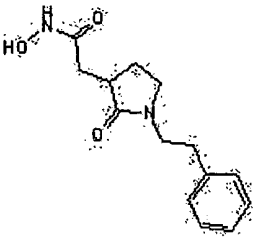
Example 26. Preparation of 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-pyrrolidin-3-yl]-N-hydroxy-acetamide (26s)

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-pyrrolidin-3-yl]-N-hydroxy-acetamide (26s) was prepared by the similar procedure described in above Example 25 (*See* Table 5).

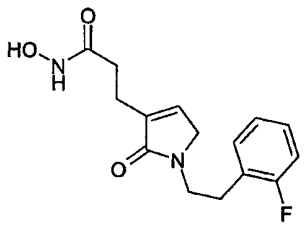
Example 27. Preparation of N-hydroxy-2-(2-oxo-1-phenethyl-pyrrolidin-3-yl)-acetamide (27s)

N-hydroxy-2-(2-oxo-1-phenethyl-pyrrolidin-3-yl)- acetamide (27s) was prepared by the similar procedure described in above Example 25 (*See* Table 5).

[Table 5]

Example	Chemical structure	NMR spectrum data
26		7.10 (t, J= 9.3 Hz, 1H), 6.44 (t, J= 2.6 Hz, 2H), 4.43 (dd, J= 14.3 Hz, 14.8 Hz, 2H), 3.78 (s,6H), 3.31-3.21 (m, 2H), 2.88-2.68 (m, 1H), 2.56-2.49 (m, 1H), 2.26-2.22 (m, 1H), 1.71-1.60 (m, 1H)
27		7.30-7.15 (m, 5H), 3.50(t, J= 7.1 Hz, 2H), 3.25-3.11 (m,2H), 2.86-2.66 (m, 3H), 2.57-2.44 (m, 1H), 2.32-2.21 (m, 2H), 1.77-1.62 (m, 1H)

Example 28. Preparation of 3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (28y)



Step 1. Preparation of toluen-4-sulfonate-2-(2-fluoro-phenyl)-ethyl ester (u)

1.02g of *p*-toluensulfonyl chloride (5.35mM), 1.24ml of diisopropyl ethylamine (7.13mM) and 86mg of 4-(dimethylamino)pyridine (0.71mM) were added to the reaction solution (3.57mM) containing 500mg of 2-(2-fluoro-phenyl)-ethanol (3.57 mM) dissolved in methylene chloride solution with stirring for 6 hrs at 0 °C under Ar atmosphere, and then the reaction mixture was stirred for 12hrs at room temperature. The resulting mixture was neutralized with ammonium chloride, extracted with ethyl acetate and washed with saturated NaCl solution to separate into an organic layer and water layer. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:7) as an

eluant to give 740 mg of toluen-4-sulfonate-2-(2-fluoro-phenyl)-ethyl ester (u) (yield : 70%).

Step 2. Preparation of allyl-[2-(2-fluoro-phenyl)-ethyl]-amine (v)

0.89ml of allylamine (11.89mM) and 0.31ml of diisopropyl ethylamine (1.78mM) were added to the reaction solution (1.19 mM) containing 350mg of toluen-4-sulfonate-2-(2-fluoro-phenyl)-ethyl ester (u) prepared by above Step 1 dissolved in acetonitrile solution with stirring for 6 hrs at 80 °C. After the reaction mixture was neutralized with 10% NaOH solution, the mixture was extracted with chloroform, washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 141 mg of allyl-[2-(2-fluoro-phenyl)-ethyl]-amine (v) (yield : 66%).

Step 3. Preparation of 4-{allyl-[2-(3-fluoro-phenyl)-ethyl]-carbamoyl}-pent-4-enoic acid methyl ester (w)

106 mg of 2-methylene-pentane dionate-5-methyl ester (0.67 mM), 139mg of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (0.73 mM) and 20mg of 4-(dimethylamino)pyridine (0.17 mM) were added to reaction solution (0.56mM) dissolving 100mg of allyl-[2-(2-fluoro-phenyl)-ethyl]-amine (v) prepared by above step 2 in methylene chloride and the mixture was stirred for 10 hrs at room temperature. After the resulting mixture was washed with 5% HCl solution (10 ml), the mixture was extracted with ethylacetate, washed with saturated NaCl. And then the extracts were washed with 10ml of saturated $NaHCO_3$ solution and NaCl solution to separate into an organic layer and water layer. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:2) as an eluant to give 128 mg of 4-{allyl-[2-(3-fluoro-phenyl)-ethyl]-carbamoyl}-pent-4-enoic acid methyl ester (w) (yield : 72%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.19-7.09 (m, 1H), 7.04-6.94 (m, 3H), 5.84 -5.57 (m, 1H), 5.13 (t, J= 10.7 Hz, 4H), 5.06-4.94 (m, 2H), 3.79 (s, 2H), 3.62 (s, 4H), 3.53 (d, J= 5.4 Hz, 3H), 2.89 (d, J= 6.0 Hz, 3H)

Step 4. Preparation of 3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionic acid methyl ester (x)

100mg of 4-{allyl-[2-(3-fluoro-phenyl)-ethyl]-carbamoyl}-pent-4-enoic acid methyl ester (w) (0.31mM) prepared by the above Step 3 was added to the catalyst solution containing 27mg of ruthenium catalyst (0.03mM) dissolved in 31.3ml of CH_2Cl_2 under Ar atmosphere. Then the mixture was stirred for 24 hrs at room temperature, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:1) as an eluant to give 69 mg of 3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionic acid methyl ester (x) (yield : 75%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.16-7.12 (m, 2H), 7.03-6.93 (m, 2H), 6.59 (br t, 1H), 3.67 -3.65 (m, 4H), 3.62 (s, 3H), 2.89 (t, J= 7.3 Hz, 2H), 2.56 (s, 4H)

Step 5. Preparation of 3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (28y)

38mg of 3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionic acid methyl ester (x) prepared by the above Step 4 was dissolved in methanol solution (0.13 mM) and then 1.7 M methanolic suspension solution containing NH_2OK (0.38 ml, 0.65 mM) was added thereto at 0°C and the resulting mixture was stirred for 8 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10% methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 25 mg of 3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (28y) (yield : 65%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.19-7.08 (m, 2H), 7.02-6.92 (m, 2H), 6.69 (br t, 1H), 3.69 (s, 2H), 3.63 (t, J= 7.0 Hz, 2H), 2.87 (t, J= 7.0 Hz, 2H), 2.51 (t, J= 7.0 Hz, 2H), 2.25 (t, J= 7.3 Hz, 2H)

Example 29. Preparation of 3-{1-[2-(3-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (29y)

3-{1-[2-(3-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (29y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

Example 30. Preparation of 3-{1-[2-(4-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (30y)

3-{1-[2-(4-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (30y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

Example 31. Preparation of N-hydroxy-3-{1-[2-(2-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (31y)

N-hydroxy-3-{1-[2-(2-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (31y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

Example 32. Preparation of N-hydroxy-3-{1-[2-(3-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (32y)

N-hydroxy-3-{1-[2-(3-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (32y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

Example 33. Preparation of N-hydroxy-3-{1-[2-(4-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (33y)

N-hydroxy-3-{1-[2-(4-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (33y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

Example 34. Preparation of 3-{1-[2-(2-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (34y)

3-{1-[2-(2-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (34y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

Example 35. Preparation of 3-{1-[2-(4-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (35y)

3-{1-[2-(4-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (35y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

Example 36. Preparation of N-hydroxy-3-{1-[2-(2-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (36y)

N-hydroxy-3-{1-[2-(2-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (36y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

Example 37. Preparation of N-hydroxy-3-{1-[2-(3-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (37y)

N-hydroxy-3-{1-[2-(3-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (37y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

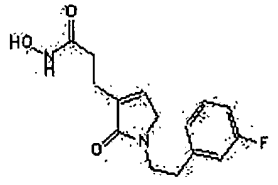
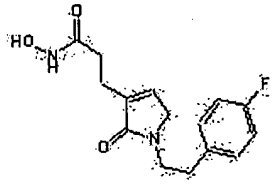
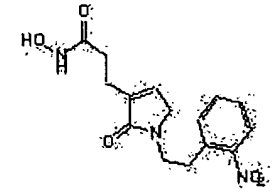
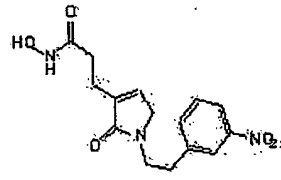
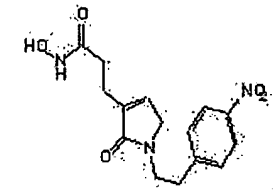
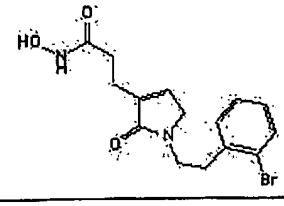
Example 38. Preparation of N-hydroxy-3-{1-[2-(4-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (38y)

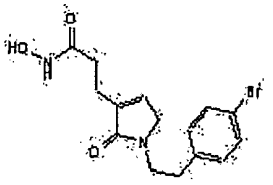
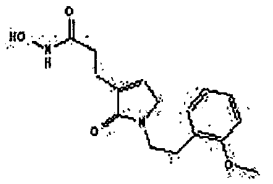
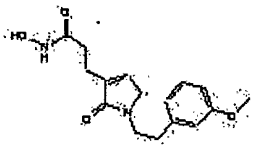
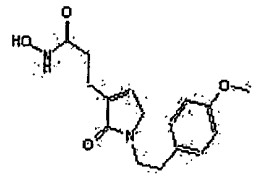
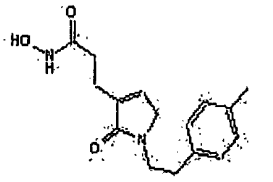
N-hydroxy-3-{1-[2-(4-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (38y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

Example 39. Preparation of N-hydroxy-3-[2-oxo-1-(2-*p*-tolyl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (39y)

N-hydroxy-3-[2-oxo-1-(2-*p*-tolyl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (39y) was prepared by the similar procedure described in above Example 28 (*See* Table 6).

[Table 6]

Example	Chemical structure	NMR spectrum data
29		7.25-7.18 (m, 1H), 6.90 (ab, J= 18.3 Hz, 4.3 Hz, 3H), 6.71 (br t, 1H), 3.65 (t, J= 6.9 Hz, 4H), 2.85 (t, J= 6.9 Hz, 2H), 2.61 (s, 2H), 2.45 (s, 2H)
30		7.11-6.94 (m, 4H), 6.70 (br t, 1H), 3.65 (s, 4H), 2.82 (s, 3H), 2.68-2.60 (m, 3H)
31		7.93 (d, J= 7.8 Hz, 1H), 7.56 (t, J= 6.7 Hz, 1H), 7.44-7.36 (m, 2H), 6.81 (br t, 1H), 3.85 (s, 2H), 3.76 (t, J= 7.3 Hz, 2H), 3.15 (t, J= 7.1 Hz, 2H), 2.54 (t, J= 7.1 Hz, 2H), 2.30 (t, J= 7.4 Hz, 2H)
32		8.00 (d, J= 7.2 Hz, 2H), 7.49-7.38 (m, 2H), 6.70 (br t, 1H), 3.72 (s, 2H), 3.64 (t, J= 7.2 Hz, 2H), 2.93 (t, J= 7.4 Hz, 2H), 2.48 (t, J= 7.3 Hz, 2H), 2.22 (t, J= 7.7 Hz, 2H)
33		8.09 (d, J= 8.4 Hz, 2H), 7.36 (d, J= 9.6 Hz, 2H), 6.74 (br t, 1H), 3.76 (d, J= 1.2 Hz, 1H), 3.69(t, J= 7.1Hz, 1H), 3.29 (d, J= 7.8 Hz, 1H), 3.26 (dd, J= 1.8 Hz, 1.5 Hz, 1H), 2.97 (t, J= 7.3 Hz, 2H), 2.49 (t, J= 6.9 Hz, 2H), 2.25 (t, J= 7.6 Hz, 2H)
34		7.48 (d, J= 8.1 Hz, 2H), 7.21-7.13 (m, 2H), 7.07-7.02 (m, 1H), 6.71 (br t, 1H), 3.70-3.62 (m, 4H), 2.98 (t, J= 7.3 Hz, 2H), 2.52 (t, J= 7.3 Hz, 2H), 2.27 (t, J= 7.6 Hz, 2H)

Example	Chemical structure	NMR spectrum data
35		7.40 (d, J= 8.4 Hz, 2H), 7.10 (d, J= 8.1 Hz, 2H), 6.79 (br t, 1H), 3.78 (d, J= 1.2 Hz, 2H), 3.66 (t, J= 7.3 Hz, 2H), 2.85 (t, J= 7.1 Hz, 2H), 2.54 (t, J= 7.1 Hz, 2H), 2.30 (t, J= 7.4 Hz, 2H)
36		7.19-7.13 (m, 1H), 7.03-7.01 (m, 1H), 6.81(t, J= 7.4 Hz, 2H), 6.70 (br t, 1H), 3.78(s, 3H), 3.69 (s, 2H), 3.63 (t, J= 7.0 Hz, 2H), 2.85 (t, J= 7.1 Hz, 2H), 2.52 (t, J= 7.7 Hz, 2H), 2.27 (t, J= 7.6 Hz, 2H)
37		7.14(t, J= 7.6 Hz, 1H), 6.72-6.67 (m, 4H), 3.72 (s, 3H), 3.65 (s, 2H), 3.60 (br t, 2H), 2.80 (t, J= 7.1 Hz, 2H), 2.51 (t, J= 7.3 Hz, 2H), 2.25 (t, J= 7.3 Hz, 2H)
38		7.02 (d, J= 8.7 Hz, 2H), 6.76 (d, J= 8.4 Hz, 2H), 6.66 (br t, 1H), 3.72 (s, 3H), 3.62-3.56 (m, 4H), 2.76 (t, J= 7.3 Hz, 2H), 2.51 (t, J= 7.3 Hz, 2H), 2.25 (t, J= 7.6 Hz, 2H)
39		7.05 (s, 4H), 6.74 (br t, 1H), 3.72 (d, J= 1.2 Hz, 2H), 3.64 (t, J= 7.3 Hz, 2H), 3.31-3.29 (m, 2H), 2.82 (t, J= 7.3 Hz, 2H), 2.54 (t, J= 7.1 Hz, 2H), 2.31 (d, J= 7.8 Hz, 2H), 2.27 (s, 3H),

Example 40. Preparation of N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (40ah)

Step 1. Preparation of 3-*p*-tolyl-acrylic acid methyl ester (40aa)

1g of *p*-tolualdehyde (8.3mM) and 4.16g of triphenyl phosphanyliden-acetic acid methyl ester (12.45mM) were dissolved in methylene chloride, the reaction solution was stirred at 90°C for overnight. After the resluting mixture was concentrated under reduced pressure, a solvent mixture mixed with EtOAc and hexane(1:7) was added thereto with stirring for 1hr. And then white solid was removed on filter, the residue was filtered and concentrated *in vacuo* to give 1.39g of 3-*p*-tolyl-acrylic acid methyl ester (40aa) (yield : 95%).

Step 2. Preparation of 3-*p*-tolyl-propionic acid methyl ester (40ab)

1.39g of 3-*p*-tolyl-acrylic acid methyl ester (40aa) prepared by above Step 1 was dissolved in methanol solution (7.9 mM) under nitrogen atmosphere. Then Pd-C was added thereto, hydrogenated under a hydrogen balloon for 1 to 2 hrs at room temperature. The reaction mixture was filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexane (1:10) as an eluant to give 1.24g of 3-*p*-tolyl-propionic acid methyl ester (40ab) (yield : 95%).

Step 3. Preparation of 3-*p*-tolyl-propane-1-ol (40ac)

1.24g of 3-*p*-tolyl-propionic acid methyl ester (40ab) prepared by above Step 2 was dissolved in 100 ml of tetrahydrofuran under Ar atmosphere. Then 27ml of lithium alluminium-hydride was added thereto with stirring for 2hrs at 0°C. After 3ml of distilled water, 3ml of NaOH (1N) and 9ml of distilled water were added to the reaction mixture sequentially, the mixture was stirred for 30min and filtered using cellite in glass filter and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:2) as an eluant to give 971mg of 3-*p*-tolyl-propane-1-ol (40ac) (yield : 93%).

Step 4. Preparation of toluene-4-sulfonate-3-*p*-tolyl-propyl ester (40ad)

2.46g of tosyl chloride (13 mM), 3.4ml of diisopropylamine (19.4 mM) and 158mg of 4-(dimethylamino)pyridine (1.29 mM) were added to reaction solution (6.46mM) dissolving 971mg of 3-*p*-tolyl-propane-1-ol (40ac) prepared by above step 3 in methylene chloride at 0°C under Ar atmosphere with stirring for 6hrs, and the reaction mixture was stirred for 12 hrs at room temperature. After the reaction mixture was neutralized with ammonium chloride, the mixture was extracted with ethyl acetate, washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:7) as an eluant to give 1.3g of toluene-4-sulfonate-3-*p*-tolyl-propyl ester (40ad) (yield : 70%).

Step 5. Preparation of allyl-(3-*p*-tolyl-propyl)-amine (40ae)

1.6ml of allylamine (21.4mM) and 0.97ml of diisopropyl ethylamine (5.5mM) were added to the reaction solution (4.27 mM) containing 1.3g of allyl-(3-*p*-tolyl-propyl)-amine (40ae) prepared by above Step 4 dissolved in acetonitrile solution with stirring for 6 hrs at 100 °C. After the reaction mixture was neutralized with 10% NaOH

solution, the mixture was extracted with chloroform, washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 687 mg of allyl-(3-*p*-tolyl-propyl)-amine (40ae) (yield : 85%).

Step 6. Preparation of 4-[allyl-(3-*p*-tolyl-propyl)-carbamoyl]-pent-4-enoic acid methyl ester (40af)

683 mg of 2-methylene-pentane dionate-5-methyl ester (4.3 mM), 902mg of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (4.7 mM) and 133mg of 4-(dimethylamino)pyridine (1.09 mM) were added to reaction solution (3.62mM) dissolving 687mg allyl-(3-*p*-tolyl-propyl)-amine (40ae) prepared by above step 5 in 0.5M of methylene chloride solution under Ar atmosphere and the mixture was stirred for 10 hrs at room temperature. After the resulting mixture was washed with 5% HCl solution (10 ml), the mixture was extracted with ethylacetate, washed with saturated NaCl. And then the extracts were washed with saturated 10ml of $NaHCO_3$ solution and NaCl solution to separate into an organic layer and water layer. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:2) as an eluant to give 797 mg of 4-[allyl-(3-*p*-tolyl-propyl)-carbamoyl]-pent-4-enoic acid methyl ester (40af) (yield : 73%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ7.05(s, 4H), 5.70(s, 1H), 5.16-5.07(m, 4H), 3.94(s, 2H), 3.64(t, J=3.3Hz, 3H), 3.36(s, 2H), 2.67-2.51(m, 6H), 2.28(s, 3H), 1.83(t, J=7.7Hz, 2H)

Step 7. Preparation of 3-[2-oxo-1-(3-*p*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (40ag)

797mg of 4-[allyl-(3-*p*-tolyl-propyl)-carbamoyl]-pent-4-enoic acid methyl ester (40af) (2.6mM) prepared by the above Step 6 was added to the catalyst solution containing 180mg of ruthenium catalyst (0.1mM) dissolved in 200ml of CH_2Cl_2 under Ar atmosphere. Then the mixture was stirred for 24 hrs at room temperature, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:1) as an eluant to give 391 mg of 3-[2-oxo-1-(3-*p*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (40ag) (yield : 50%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.96 (s, 4H), 6.56 (s, 1H), 3.67 (s, 2H), 3.55 (s, 3H), 3.37 (t, *J*= 7.2 Hz, 2H), 2.48 (t, *J*= 8.2 Hz, 6H), 2.19 (s, 3H), 1.76 (t, *J*= 7.6 Hz, 2H)

Step 8. Preparation of N-hydroxy-3-[2-oxo-1-(3-*p*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (40ah)

100mg of 3-[2-oxo-1-(3-*p*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (40ag) prepared by the above Step 7 was dissolved in methanol solution (0.33 mM) and then 1.7 M methanolic suspension solution containing NH_2OK (0.82 ml, 5.0 mM) was added thereto at 0°C and the resulting mixture was stirred for 8 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10% methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 50 mg of N-hydroxy-3-[2-oxo-1-(3-*p*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (40ah) (yield : 50%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.21 (s, 4H), 6.95 (s, 1H), 3.96 (s, 2H), 3.60 (s, 2H), 2.72 (s, 5H), 2.45 (s, 3H), 1.99 (s, 2H)

Example 41. Preparation of N-hydroxy-3-[2-oxo-1-(3-*o*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (41ah)

N-hydroxy-3-[2-oxo-1-(3-*o*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (41ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

Example 42. Preparation of N-hydroxy-3-[2-oxo-1-(3-m-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (42ah)

N-hydroxy-3-[2-oxo-1-(3-m-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (42ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

Example 43. Preparation of N-hydroxy-3-{1-[3-(4-isopropyl-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (43ah)

N-hydroxy-3-{1-[3-(4-isopropyl-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (43ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

Example 44. Preparation of 3-{1-[3-(4-bromo-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (44ah)

3-{1-[3-(4-bromo-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (44ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

Example 45. Preparation of 3-{1-[3-(4-chloro-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (45ah)

3-{1-[3-(4-chloro-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (45ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

Example 46. Preparation of N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (46ah)

N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (46ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

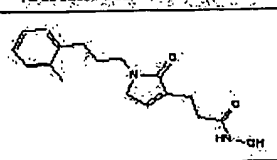
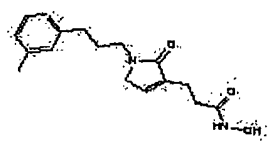
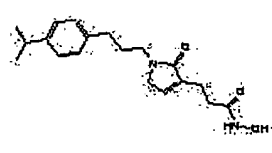
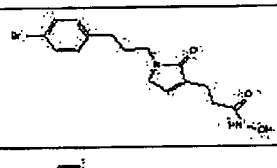
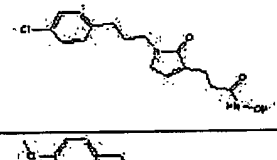
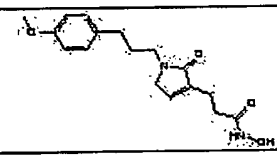
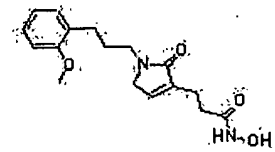
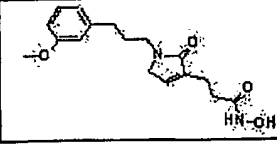
Example 47. Preparation of N-hydroxy-3-{1-[3-(2-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (47ah)

N-hydroxy-3-{1-[3-(2-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (47ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

Example 48. Preparation of N-hydroxy-3-{1-[3-(3-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (48ah)

N-hydroxy-3-{1-[3-(3-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (48ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

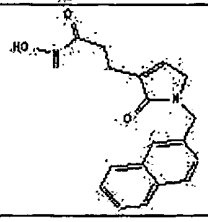
[Table 7]

Example	Chemical structure	NMR spectrum data
41		7.08 (d, J= 4.2 Hz, 4H), 6.69 (s, 1H), 3.80 (s, 2H), 3.48 (d, J= 6.6 Hz, 2H), 2.57 (d, J= 9.0 Hz, 6H), 2.25 (d, J= 6.3 Hz, 4H), 1.79 (s, 2H)
42		7.02-6.97 (m, 1H), 6.81 (d, J= 8.4 Hz, 3H), 6.64 (s, 1H), 4.07 (s, 2H), 3.71 (s, 2H), 3.32 (t, J= 7.4 Hz, 2H), 2.43 (t, J= 7.7Hz, 5H), 2.17 (t, J= 6.5 Hz, 4H), 1.78-1.68 (m, 2H)
43		10.23 (s, 1H), 7.09 (dd, J= 6.0 Hz, 4H), 6.73 (s, 1H), 3.79 (s, 2H), 3.45 (t, J= 5.1 Hz, 2H), 2.87-2.80 (m, 1H), 2.61 (s, 1H), 2.56 (t, J= 5.9 Hz, 2H), 2.46 (s, 2H), 1.88-1.81 (m, 2H), 1.26-1.19 (m, 6H)
44		7.23 (t, J= 5.5 Hz, 1H), 7.14 (t, J= 5.5 Hz, 3H), 6.73 (s, 1H), 3.77 (s, 2H), 3.43 (t, J= 5.0 Hz, 2H), 2.58 (t, J= 5.7 Hz, 4H), 2.45 (s, 2H), 1.88-1.81 (m, 2H)
45		7.23-7.04 (m, 4H), 6.73 (s, 1H), 3.77 (s, 2H), 3.43 (t, J= 5.7 Hz, 2H), 2.56 (t, J= 12.9 Hz, 3H), 2.42 (s, 2H), 1.83 (t, J= 6.7 Hz, 2H)
46		7.03 (d, J= 8.7 Hz, 2H), 6.79-6.75 (m, 2H), 6.72 (s, 1H), 3.72 (d, J= 9.9 Hz, 5H), 3.40 (t, J= 7.3 Hz, 2H), 2.58-2.42 (m, 6H), 1.78 (t, J= 7.4 Hz, 2H)
47		7.16-7.06 (m, 2H), 6.84-6.67 (m, 3H), 3.79 (t, J= 5.5 Hz, 2H), 3.75 (t, J= 3.4Hz, 3H), 3.50-3.41 (m, 2H), 2.55 (t, J= 7.7Hz, 3H), 2.43 (s, 1H), 1.87 (s, 2H), 1.84-1.77 (m, 2H)
48		7.19-7.10 (m, 1H), 6.71 (d, J= 10.8Hz, 4H), 3.75 (s, 5H), 3.49-3.40 (m, 2H), 2.55 (t, J= 7.7Hz, 4H), 2.43 (s, 2H), 1.88-1.84(m, 2H)

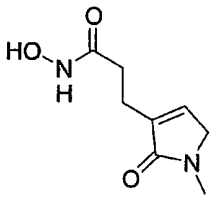
Example 49. Preparation of N-hydroxy-3-(1-naphthalene-2-ylmethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (1e')

N-hydroxy-3-(1-naphthalene-2-ylmethyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (1e') was prepared by the similar procedure described in above Example 1 (*See* Table 8).

[Table 8]

Example	Chemical structure	NMR spectrum or LC-MS data
49		RT : 3.93-5.93 (Mass : 311.2)

Example 50. Preparation of N-hydroxy-3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (2h')



Step 1. Preparation of 3-(2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid methyl ester (2f)

0.1ml of triethylsilane (0.63mM) was added to the reaction solution containing 200mg of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (0.63 mM) dissolved in 0.7ml of trifluoroacetic acid solution at 0°C. After the reaction mixture was heated for 1hr, the mixture was filtered and concentrated *in vacuo* to remove solvent. Then the resulting mixture was dissolved in 20ml of chloroform solution to separate into an organic layer and water layer. The organic layer was washed with 5ml of saturated $NaHCO_3$ solution and 5ml of saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (19:1) as an eluant to give 50 mg of 3-(2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid methyl ester (2f) (yield : 47%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.76 (br t, 1H), 3.89 (d, J= 1.3 Hz, 2H), 3.63 (t, J= 1.9 Hz, 3H), 2.58 (s, 4H)

Step 2. Preparation of 3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid methyl ester (2g)

0.33ml of NaHMDS solution (1.0 M in THF, 0.33mM) was added to 0.6ml of THF solution containing 50mg of 3-(2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid

methyl ester (2f) (0.295mM) prepared by the Step 1 in a dropwise manner at -79°C and stirred for 30 mins. After 0.3ml of dimethyl sulfate 0.359mM) was added thereto, the reaction mixture was stirred for 4hrs at 0°C. Then the resulting mixture was dissolved in 2ml of saturated NH_4Cl solution and extracted with 7ml of ethyl acetate to separate into an organic layer and water layer. The organic layer was washed with 2ml of saturated $NaHCO_3$ solution and 2ml of saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with EtOAc as an eluant to give 18 mg of 3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid methyl ester (2g) (yield : 33%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.65 (br t, 1H), 3.81 (s, 1H), 3.64 (s, 3H), 3.01 (s, 3H), 2.60 (t, 4H).

Step 3. Preparation of N-hydroxy-3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (2h)

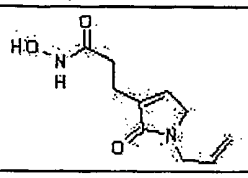
18mg of 3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid methyl ester (2g) prepared by the above Step 2 was dissolved in methanol solution (0.1 mM) and then 1.7 M methanolic suspension solution containing NH_2OK (0.09 ml, 0.15 mM) was added thereto at 0°C and the resulting mixture was stirred for 1 hr at room temperature. The resulting mixture was neutralized with 0.03 ml of acetic acid, diluted with 10% methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and methanol (5:2) as an eluant to give 11 mg of N-hydroxy-3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (2h) (yield : 59%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.76 (br t, 1H), 3.84 (s, 2H), 3.00 (s, 3H), 2.59 (t, J= 7.2 Hz, 2H), 2.42 (t, J= 7.2 Hz, 2H)

Example 51. Preparation of 3-(1-allyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide (3h')

3-(1-allyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide (3h') was prepared by the similar procedure described in above Example 50 (*See* Table 9).

[Table 9]

Example	Chemical structure	NMR spectrum data
51		6.89 (br t, 1H), 5.98-5.67 (m, 2H), 5.10-5.08 (m, 1H), 3.36 (t, J= 1.8Hz, 2H), 2.61 (s, 2H), 2.06 (s, 2H), 1.87 (s, 2H)

Example 52. Preparation of N-hydroxy-3-[1-(2-naphthalene-1-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (4n')

N-hydroxy-3-[1-(2-naphthalene-1-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (4n') was prepared by the similar procedure described in above Example 28 (*See* Table 10).

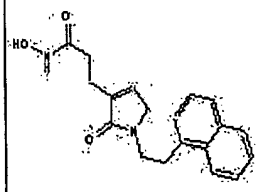
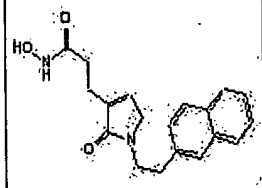
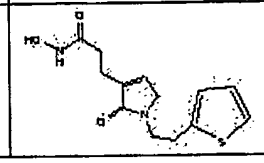
Example 53. Preparation of N-hydroxy-3-[1-(2-naphthalene-2-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (5n')

N-hydroxy-3-[1-(2-naphthalene-2-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (5n') was prepared by the similar procedure described in above Example 28 (*See* Table 10).

Example 54. Preparation of N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (6n')

N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (6n') was prepared by the similar procedure described in above Example 28 (*See* Table 10).

[Table 10]

Example	Chemical structure	NMR spectrum data
52		8.01(d, J= 8.1 Hz, 1H), 7.77(d, J= 8.7 Hz, 1H), 7.66 (d, J= 8.1 Hz, 1H), 7.48-7.20 (m, 4H), 6.62 (br t, 1H), 3.56 (s, 2H), 3.30-3.25(m, 2H), 2.51 (t, J= 7.3 Hz, 2H), 2.25 (t, J= 7.3 Hz, 2H)
53		7.73-7.66 (m, 3H), 7.53 (s, 1H), 7.40-7.32 (m, 2H), 7.22 (s, 1H), 6.61 (br t, 1H), 3.69 (t, J= 7.3 Hz, 2H), 3.60 (s, 2H), 2.97 (t, J= 7.0 Hz, 2H), 2.49 (t, J= 7.2 Hz, 2H), 2.24 (t, J= 7.3 Hz, 2H)
54		7.08 (br t, 1H), 6.85 (t, J= 4.0 Hz, 1H), 6.74 (s, 1H), 6.68 (br t, 1H), 3.65 (s, 4H), 3.37-3.29 (m, 1H), 3.05 (t, J= 6.1 Hz, 2H), 2.51 (d, J= 4.8 Hz, 2H), 2.28 (s, 1H)

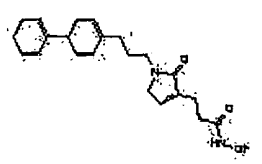
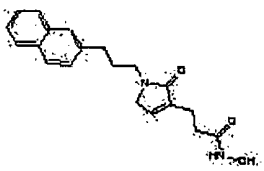
Example 55. Preparation of 3-[1-(3-biphenyl-4-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (7w')

3-[1-(3-biphenyl-4-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (7w') was prepared by the similar procedure described in above Example 40 (*See* Table 11).

Example 56. Preparation of N-hydroxy-3-[1-(3-naphthalene-2-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (8w')

N-hydroxy-3-[1-(3-naphthalene-2-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (8w') was prepared by the similar procedure described in above Example 40 (*See* Table 11).

[Table 11]

Example	Chemical structure	NMR spectrum data
55		7.51 (dd, *J*= 8.0 Hz, 4H), 7.37 (t, *J*= 7.4 Hz, 2H), 7.26 (q, *J*= 7.2 Hz, 3H), 6.81 (s, 1H), 4.79 (s, 2H), 3.89 (s, 2H), 3.48 (t, *J*= 7.1 Hz, 2H), 2.64 (t, *J*= 7.7 Hz, 2H), 2.56 (t, *J*= 5.1 Hz, 2H), 2.32 (t, *J*= 6.9 Hz, 1H)
56		10.54 (s, 1H), 7.71 (dd, *J*= 7.9 Hz, 3H), 7.54 (s, 1H), 7.41-7.33 (m, 2H), 7.24(d, *J*= 7.8 Hz, 1H), 6.64 (s, 1H), 3.67 (s, 2H), 3.40 (s, 2H), 2.69 (t, *J*= 6.7 Hz, 2H), 2.57 (s, 2H), 2.41 (s, 2H), 1.86 (s, 2H)

Example 57. Preparation of 3-[1-(2,4-Dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydropyridin-3-yl]N-hydroxypropionamide(e1)

Step 1. Preparation of But-3-enyl-(2,4-dimethoxybenzyl)amine (b)

0.5ml of 1-Bromo-3-butene (4.926mM) and 0.94 ml of diisopropyl ethylamine (5.396 mM) were added to the reaction solution containing 0.74ml of 2, 4-dimethoxybenzylamine(a) (4.926 mM) dissolved in methylene chloride with stirring and the solution was left alone at room temperature for overnight. The reaction mixture was washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with EtOAc solvent as an eluant to give 436mg of the pure title compound (b) (yield: 40%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.10(d, *J*=8.1 Hz, 1H), 6.41(m, 2H), 5.75(m, 1H), 5.01(m, 2H), 3.78(s, 3H), 3.77(s, 3H), 3.70(s, 2H), 2.63(t, *J*=7.5 Hz, 2H), 2.24(m, 2H)

Step 2. Preparation of 4-[But-3-enyl-(2,4-dimethoxybenzyl)-carbamoyl]-pent-4-enoic acid methyl ester (c)

714 mg of 2-methylene-pentane dionate-5-methyl ester (4.519 mM), 953mg of EDC (4.971 mM) and 110mg of DMAP (0.9 mM) were added to 0.5 M of reaction solution dissolving the compound (b) prepared by above step 1 in methylene chloride and the mixture was stirred for 5 hrs at room temperature. The resulting mixture was diluted with ethyl acetate and washed with 5% HCl solution (10 ml) and 10ml of sat. $NaHCO_3$ solution to separate into an organic layer and water layer. The organic layer

was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:2) as an eluant to give 1.39 g of 4-[but-3-enyl-(2,4-dimethoxybenzyl)-carbamoyl]-pent-4-enoic acid methyl ester (c) (yield : 40%).

Step 3. Preparation of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (d)

130mg of the compound (c) (0.360 mM) prepared by the above Step 2 was added to the catalyst solution containing 20mg of ruthenium (0.024 mM) dissolved in CH_2Cl_2. Then the mixture was stirred for 24 hrs at room temperature, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with methanol/chloroform (1:10) solvent mixture as an eluant to give 108 mg of the title compound (d) (yield : 90%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.17(d, J=8.9Hz, 1H), 6.41(m, 2H), 6.26(t, J=4.3 Hz, 1H), 4.53(s, 2H), 3.77(s, 3H), 3.76(s, 3H), 3.62(s, 3H), 3.28(t, J=7.1 Hz, 2H), 2.61-2.47(m, 4H), 2.22(m, 2H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.6, 164.8, 160.2, 158.5, 134.2, 133.9, 130.4, 118.0, 104.1, 98.3, 55.2, 51.3, 45.0, 44.3, 33.3, 26.6, 23.9

Step 4. Preparation of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-propionamide (e1)

46mg of compound (d) prepared by the above Step 3 was dissolved in methanol solution (0.138 mM) and then 1,7 M methanolic suspension solution containing NH_2OK (0.122 ml, 0.207 mM) was added thereto at 0°C and the resulting mixture was stirred for 3 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10 ml of ethyl acetate solution, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:10) solvent mixture as an eluant to give 32 mg of the title compound (e1) (yield: 73%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.122(d, J=9.0 Hz, 1H), 6.415-6.331 (m, 3H), 4.505 (s, 2H), 3.750 (s, 3H), 3.744 (s, 3H), 3.271 (t, J=6.9 Hz, 2H), 2.552 (m, 2H), 2.381 (m, 2H), 2.220 (m, 2H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.1, 165.4, 160.2, 158.5, 135.8, 133.5, 130.4, 117.5, 104.2, 98.3, 55.3, 44.9, 44.6, 32.8, 27.1, 23.8

Example 58. Preparation of N-hydroxy-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (e2)

N-hydroxy-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (e2) was prepared by the similar procedure described in above Example 57 (*See* Table 12).

Example 59. Preparation of N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (e3)

N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (e3) was prepared by the similar procedure described in above Example 57 (*See* Table 12).

Example 60. Preparation of 3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy propionamide (e4)

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy propionamide (e4) was prepared by the similar procedure described in above Example 57 (*See* Table 12).

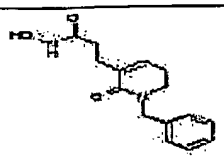
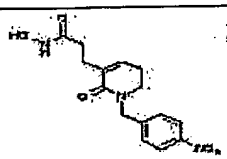
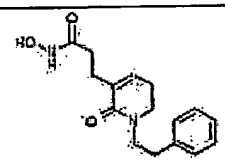
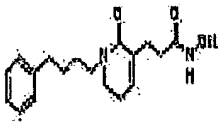
Example 61. Preparation of N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide (e5)

N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide (e5) was prepared by the similar procedure described in above Example 57 (*See* Table 12).

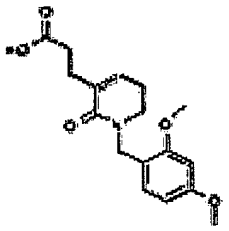
Example 62. Preparation of N-hydroxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (e6)

N-hydroxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (e6) was prepared by the similar procedure described in above Example 57 (*See* Table 12).

[Table 12]

Example	Chemical structure	NMR spectrum data
58		7.28(m, 5H), 6.44(t, J=4.3 Hz, 1H), 4.61(s, 2H), 3.33(m, 2H), 2.57(t, J=7.5 Hz, 2H), 2.28(m, 4H)
59		8.14(d J=8.4Hz 2H), 7.40(t J=7.2Hz 2H), 6.42(br t 1H), 4.67(s 2H), 3.32(t J=6.3Hz 2H), 2.67-2.32(m 6H)
60		7.29-7.18(m 5H) 6.40(br t 1H), 3.62(t J=7.2Hz 2H), 3.19(t J=7.1Hz 2H), 2.85(t J=7.1Hz 2H), 2.54-2.44(m 2H), 2.18-2.15(m 4H)
61		7.24-7.11(m, 5H), 6.31(br t, 1H), 3.35(br t, 2H), 3.23(br t, 2H), 2.55(d, J=6.6Hz, 4H), 2.33(s, 2H), 2.18(s, 2H), 1.80(br t, 2H)
62		7.28-7.13(m, 5H), 6.36(t, J=3.9, 1H), 3.39(t, J=6.75, 2H), 3.29(t, J=7.05, 2H), 2.62(t, J=7.05, 2H), 2.54(t, J=6.75, 2H) 2.40(t, J=6.75, 2H), 2.27(ab, J=6.0, 5.4, 2H), 1.58(t, J=2.7, 4H)

Example 63. Preparation of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f1)



11mg of $LiOH \cdot H_2O$ solution (0.262 mM) was added to 0.75ml of THF solution containing 58mg of 3-[1-(2,4-dimethoxy benzyl)-2-oxo-1,2,5,6-tetrahydro pyridine-3-yl]-propionic acid methyl ester (d) (0.174 mM) in a dropwise manner at 0°C. After the reaction mixture was stirred for 2hrs at 0°C and for 1hr at room temperature, 5% HCl was added to the mixture to pH 2. Then the mixture was extracted three times with

10ml of ethyl acetate, the organic layer was washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with methanol/chloroform (1:10) solvent mixture as an eluant to give 44 mg of the title compound (f1) (yield : 80%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.16(d, J=8.9 Hz, 1H), 6.42(m, 2H), 6.29(t, J=4.3 Hz, 1H), 4.54(s, 2H), 3.76(s, 3H), 3.76(s, 3H), 3.29(t, J=7.2 Hz, 2H), 2.56(m, 4H), 2.22(m, 2H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 177.7, 165.1, 160.1, 158.5, 134.6, 133.9, 130.5, 117.7, 104.1, 98.3, 55.2, 44.9, 44.5, 33.5, 26.3, 23.8

Example 64. Preparation of 3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f2)

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f2) was prepared by the similar procedure described in above Example 63 (*See* Table 13).

Example 65. Preparation of 3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f3)

3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f3) was prepared by the similar procedure described in above Example 63 (*See* Table 13).

Example 66. Preparation of 3-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f4)

3-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f4) was prepared by the similar procedure described in above Example 63 (*See* Table 13).

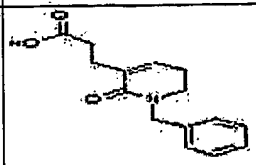
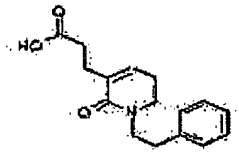
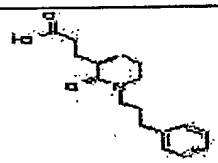
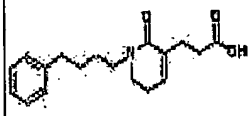
Example 67. Preparation of 3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f5)

3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f5) was prepared by the similar procedure described in above Example 63 (*See* Table 13).

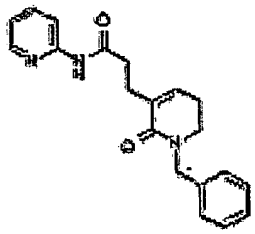
Example 68. Preparation of 3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f6)

3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f6) was prepared by the similar procedure described in above Example 63 (*See* Table 13).

[Table 13]

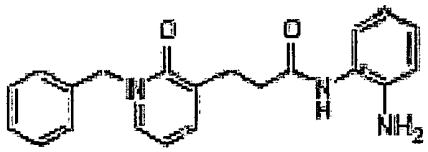
Example	Chemical structure	NMR spectrum data
64		7.25(m, 5H), 6.34(t, J=4.2Hz, 1H), 4.60(s, 2H), 3.26(t, J=7.1 Hz, 2H), 2.59(m, 4H), 2.25(m, 2H)
65		8.16(d J=8.7Hz 2H), 7.42(d, J=8.6Hz, 2H), 6.39(t J=4.3Hz, 1H) 4.69(s, 2H) 3.32(t, J=7.2Hz, 2H) 2.64-2.53(m, 4H), 2.33(dd J=6.9Hz, 5.7Hz, 2H)
66		9.92(br s 1H), 7.28-7.15(m, 5H), 6.28(t, J=4.4, 1H), 3.60(t J=7.4, 2H) 3.16(t, J=7.2, 2H) , 2.84(t, J=7.4, 2H) 2.58-2.48 (m, 4H) 2.15(AB, J=11.4, 6.8, 2H)
67		7.28-7.10(m,5H), 6.28(br, t, 1H), 5.75-5.60(m, 1H), 5.01(d, J=16.5Hz, 2H), 3.41-3.26(m, 3H) 2.63-2.26(m, 7H) 1.84(t, J=6.8Hz, 2H)
68		7.256-7.138(m, 5H), 6.33(br, t, 1H), 3.42(t, J=6.9, 2H), 3.32(t, J=7.35, 2H), 2.63(t, J=7.05, 2H), 2.547(d, J=2.4, 4H), 2.30(d, J=4.5, 2H), 1.61(q, J=1.5, 4H)

Example 69. Preparation of 3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-pyridin-2-yl-propionamide (g1)



Pyridyl amine was added to organic solvent dissolving 30mg of 3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (0.12mM) in EDC. The resulting compound was purified by Silica gel column chromatography with methanol/chloroform (1:20) solvent mixture as an eluant to give 16 mg of the title compound (g1) (yield : 39%).

Example 70. Preparation of N-(2-amino-phenyl)-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g2)



40mg of 1,2-phenylenediamine (0.37 M), 77mg of EDC (0.4 M) and 1mg of DMAP (3 M%) were added to reaction solution dissolving 3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid prepared by above Example 8 in 1ml of methylene chloride under Argon atmosphere. After the mixture was stirred for 13 hrs at room temperature, the resulting mixture was diluted with ethyl acetate and washed with 10% NaOH solution (10 ml). Then the residue was extracted with 50ml of chloroform, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:20) as an eluant to give 96 mg of N-(2-amino-phenyl)-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g2) (yield : 91%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ8.29 (s, 1H), 7.29-7.19 (m, 5H), 7.13 (d, 1H, *J*=7.8Hz), 6.99-6.94 (m, 1H), 6.68 (t, 2H, *J*=7.9Hz), 6.37 (t, 1H, *J*=8.4Hz), 4.57 (t, 2H, *J*=7.4Hz), 3.88 (s, 2H), 3.29-3.21 (m, 2H), 2.68 (t, 2H, *J*=6.5Hz), 2.59 (t, 2H, 6.5Hz), 2.26-2.217 (m, 2H)

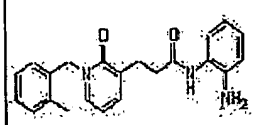
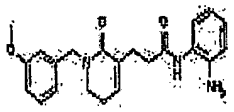
Example 71. Preparation of N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g3)

N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g3) was prepared by the similar procedure described in above Example 69 and 70 (*See* Table 14).

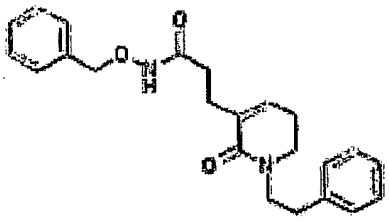
Example 72. Preparation of N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g4)

N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g4) was prepared by the similar procedure described in above Example 69 and 70 (*See* Table 14).

[Table 14]

Example	Chemical structure	NMR spectrum data
71		8.23(s,1H), 7.12(dd,5H,J=6.6Hz), 6.979(t,1H,J=7.5Hz), 6.697(t,2H,J=8.9Hz), 6.408(t,1H,J=7.4Hz), 4.602(s,2H), 3.874(s,2H), 3.239(t,2H,J=7.1Hz), 2.702(t,2H,J=6.8Hz), 2.604(t,2H,J=6.3Hz), 2.260(t,5H,J=6.3Hz)
72		8.305(s,1H), 7.189-7.091(m,2H), 6.969-6.914(m,2H), 6.794-6.741(m,3H), 6.691-6.631(m,2H), 6.355(t,1H,J=4.1Hz), 4.539(s,2H) 3.965(s,2H), 3.707(s,3H), 3.253(t,2H,J=7.0Hz), 2.661-2.539(m,4H), 2.22(dd,2H,J=7.1Hz)

Example 73. Preparation of N-benzyloxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g5)



Benzyloxyamine was added to organic solvent dissolving 30mg of 3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (0.15mM) prepared by above Example 12 in EDC. The resulting compound was purified by Silica gel column chromatography with ethylacetate/chloroform (1:1) solvent mixture as an eluant to give 41 mg of N-benzyloxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g5) (yield : 75%).

^{1}H-NMR (300 MHz, CDCl3) δ7.41-7.15 (m, 1H), 6.34 (br t, 1H), 4.88 (s, 2H), 3.58 (t, *J*=7.4Hz, 2H), 3.16 (t, *J*=7.2Hz, 2H), 2.82 (t, *J*=7.2Hz, 2H), 2.53 (t, *J*=6.8 Hz, 2H), 2.26 (br s, 1H), 2.19 (dd, *J*=11.4, 7.1Hz, 2H)

Example 18. Preparation of 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide (j1)

Step 1. Preparation of 3-[1-(4-amino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (h)

50mg of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (d) (0.16 mM) prepared by the Step 3 of above Example 1 was dissolved in methanol solution at room temperature. Then 154mg of Zn (2.36mM) and 0.01ml of acetic acid (0.16 mM) were added thereto and the mixture was stirred for 20 hrs at 80°C. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with ethylacetate and hexane (1:1) as an eluant to give 43 mg of 3-[1-(4-amino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (h) (yield : 92%).

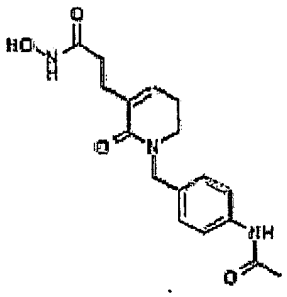
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.22 (d, 1H, J=8.5Hz), 8.11 (d, 1H, J=8.4Hz), 7.37 (t, 2H, J=8.3Hz), 6.33 (t, 1H, J=4.3Hz), 4.66 (d, 2H, J=7.5Hz), 3.63 (s, 3H), 3.29 (t, 2H, J=6.6Hz), 2.63 (t, 2H, J=6.9Hz), 2.54 (t, 2H, J=6.6Hz), 2.28 (t, 2H, J=4.2Hz)

Step 2. Preparation of 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (i)

17.5mg of 3-[1-(4-amino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (h) prepared by above Step 1 was dissolved in methylene chloride solution (0.06mM). And then 6 μl of $(AcO)_2O$(0.07 mM), 0.01ml of triethylamine (0.08mM) and 1.0mg of DMAP (0.008mM) were added thereto and the mixture was stirred for 3 hrs at 0°C. The reaction was stopped by adding methanol and the mixture was extracted three times with 10ml of ethyl acetate. The organic layer was washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with ethylacetate as an eluant to give 46 mg of 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (i) (yield : 44%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ8.34 (s, 1H), 7.40 (d, 2H, J=8.4Hz), 7.10 (d, 2H, J=8.4Hz), 6.29 (t, 1H, J=4.2Hz), 4.50 (s, 2H), 3.61 (s, 3H), 3.22 (t, 2H, J=7.1Hz), 2.59 (t, 2H, J=7.1Hz), 2.51 (d, 2H, J=6.6Hz), 2.22 (dd, 2H, J=6.9Hz), 2.09 (s, 3H)

Step 3. Preparation of 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide (j1)



3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (i) prepared by above Step 2 dissolved in organic solvent such as methanol was reacted with amine salt to give 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide (j1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50 (d J=8.0Hz 2H), 7.23 (d J=8.0Hz 2H), 6.44 (br t 1H), 4.57 (S 2H), 3.33 (t, J=6.5Hz, 6H) 2.57 (br t, 2H) 2.30-2.26 (m, 4H) 2.10 (s, 2H)

Example 75. Preparation of N-4-[5-(2-hydroxycarbamoyl-ethyl)-6-oxo-3,6-dihydro-2-pyridin-1-yl-methyl]-phenyl-benzamide (j2)

N-4-[5-(2-hydroxycarbamoyl-ethyl)-6-oxo-3,6-dihydro-2-pyridin-1-yl-methyl]-phenyl-benzamide (j2) was prepared by the similar procedure described in above Example 74 (*See* Table 15).

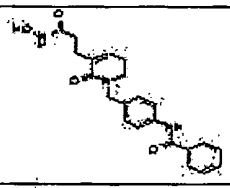
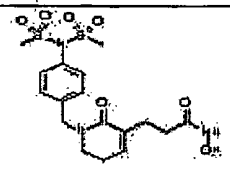
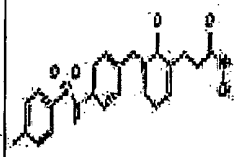
Example 76. Preparation of N-hydroxy-3-[1-(4-dimethylsulfonylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide (j3)

N-hydroxy-3-[1-(4-dimethylsulfonylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide (j3) was prepared by the similar procedure described in above Example 74 (*See* Table 15).

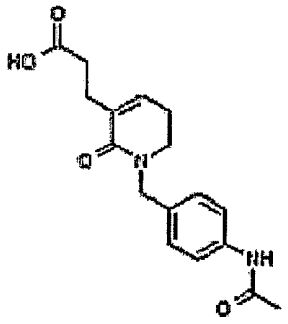
Example 77. Preparation of N-hydroxy-3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide (j4)

N-hydroxy-3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide (j4) was prepared by the similar procedure described in above Example 74 (*See* Table 15).

[Table 15]

Example	Chemical structure	NMR spectrum data
75		7.90 (t J=7.05Hz 2H), 7.67 (d, J=8.10Hz, 2H) 7.59-7.47(m, 3H) 7.30 (d J=8.10Hz 2H), 6.45 (br t, 1H) 4.61 (s,2H) 3.36 (t, J=7.2, 2H) 3.30 (q, J=1.5Hz, 4H) 2.58 (br t,2H)
76		7.24 (q, J=8.6Hz, 4H) 6.45 (br t, 1H) 4.58 (s,2 H) 3.38-3.29 (m,7H) 2.93 (s, 3H) 2.57 (t, 2H, J=7.1) 2.34-2.24(m, 4H)
77		7.78 (d, J=8.0Hz, 2H), 7.31 (d, J=7.5Hz,2H) 7.27-7.21 (m, 4H) 6.97 (t,J=7.2Hz,1H) 4.61(d, J=3.5Hz, 1H) 3.47(s, 4H) 3.3 6-3.30 (m,1H) 2.71-.264(m, 1H) 2.51-2.44 (m,3H), 2.32 (d, J=4.5Hz, 1H)

Example 78. Preparation of 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (k)



3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (i) prepared by above Step 2 of Example 18 dissolved in organic solvent such as tetrahydrofurane was reacted with LiOH to give 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (k).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50 (d J=8.0Hz 2H), 7.23 (d J=8.6Hz 2H), 6.45 (t J=4.5Hz 1H), 4.58 (S 2H), 3.32 (t, J=7.5Hz,3H) 2.57 (t, J=7.5Hz, 2H) 2.46 (t, J=7.5Hz, 2H)

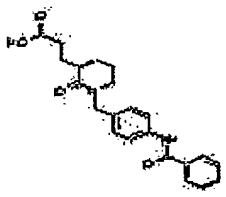
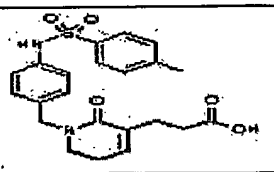
Example 79. Preparation of 3-[1-(4-benzoylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (k2)

3-[1-(4-benzoylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (k2) was prepared by the similar procedure described in above Example 78 (*See* Table 16).

Example 80. Preparation of 3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (k3)

3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (k3)was prepared by the similar procedure described in above Example 78 (*See* Table 16).

[Table 16]

Example	Chemical structure	NMR spectrum data
79		7.83 (d, J=6.9Hz, 2H), 7.59(d, J=8.4Hz, 2H), 7.49-7.37 (m, 4H), 7.19 (d, J=8.4Hz, 2H), 6.33 (q, J=4.5Hz, 1H) 3.26 (t, J=7.2Hz, 3H) 2.54-2.40 (m, 4H) 2.24 (ab, J=11.6Hz, 3.5Hz, 2H)
80		7.74(d, J=8.1Hz, 4H), 7.18 (d, J=7.8Hz,2H), 6.93 (d, J=8.1, 2H), 4.53(s, 2H), 3.20(br t,2H), 2.40 (s, 9H)

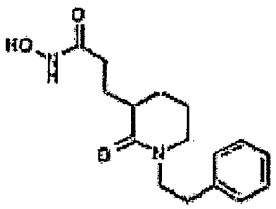
Example 81. Preparation of N-hydroxy-3-(2-oxo-1-phenethyl-piperidine-3-yl)-propionamide (m)

Step 1. Preparation of [1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-acetic acid methyl ester (l)

3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester was dissolved in alcohol solvent under nitrogen atmosphere. Then Pd-C was added thereto, and the mixture was hydrogenated under a hydrogen balloon for 1 to 2 hrs at room temperature. The reaction mixture was filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with a solvent mixture mixed with EtOAc/hexane (1:1) as an eluant to give [1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-acetic acid methyl ester (l) (yield : 74%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.13 (d, 1H, J=8.4Hz), 6.42 (d, 2H, J=7.2Hz), 4.51(ab, 2H, J=32.9, 7.4Hz), 3.76 (s, 6H), 3.66(s, 3H), 3.24-3.18(m, 2H), 2.93-2.72(m, 2H), 2.56-2.43(m, 1H), 1.98-1.55(m, 4H)

Step 2. Preparation of N-hydroxy-3-(2-oxo-1-phenethyl-piperidine-3-yl)-propionamide (m)



[1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-acetic acid methyl ester (l) prepared by above Step 1 was reacted with amine salt to give N-hydroxy-3-(2-oxo-1-phenethyl-piperidine-3-yl)-propionamide (m).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.26-7.17 (m 5H), 3.61-3.44 (m 2H) 3.08-2.83 (m 4H), 2.56-2.16 (m 4H)

Example 82. Preparation of 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p1)

Step 1. Preparation of 3-(benzyl-but-3-enyl-carbamoyl)-but-3-enoic acid methyl ester (n)

2-Methylene-pentane dionate-5-methyl ester, EDC and DMAP were added to reaction solution dissolving the but-3-enyl-(2,4-dimethoxybenzyl)amine (b) prepared by above Step 1 of Example 1 in methylene chloride and the mixture was stirred for 5 hrs at room temperature to give 3-(benzyl-but-3-enyl-carbamoyl)-but-3-enoic acid methyl ester (n).

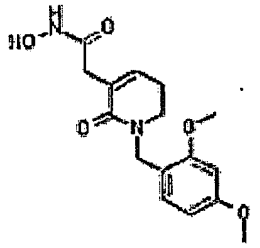
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30-7.19 (m, 5H), 5.69(br t, 1H), 5.23(s, 2H), 5.00(t, 2H, J=12.6Hz), 4.74(s, 2H), 3.61(s, 3H), 3.42(s, 4H), 2.30(q, 2H, J=7.2Hz)

Step 2. Preparation of [1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid methyl ester (o)

3-(benzyl-but-3-enyl-carbamoyl)-but-3-enoic acid methyl ester (n) prepared by above Step 1 was added to the catalyst solution containing Grubb's (I) catalysis such as ruthenium dissolved in organic solvent such as CH_2Cl_2 to give [1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid methyl ester (o).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.17 (d, 1H, J=6.2Hz), 6.42-6.36 (m, 3H), 4.54 (s, 2H), 3.76 (d, 6H, J=3.0Hz), 3.66 (s, 3H), 3.35(t, 2H, J=6.9), 3.28(s, 2H), 2.29(ab, 2H, J=11.3, 3.4Hz)

Step 3. Preparation of 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p1)



[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid methyl ester (o) prepared by above Step 2 dissolved in alcohol solvent was reacted with amine salt to give 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J=8.7Hz, 1H), 6.54(br t, 1H) 6.44 (d, J=6.0Hz, 2H), 4.55 (s, 2H), 3.78(s,6H), 3.41-3.32(m,2H), 3.20(s, 2H), 2.0 (d, J=4.5Hz, 2H)

Example 83. Preparation of 2-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide (p2)

2-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide (p2) was prepared by the similar procedure described in above Example 82 (*See* Table 17).

Example 84. Preparation of N-hydroxy-2-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide (p3)

N-hydroxy-2-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide (p3) was prepared by the similar procedure described in above Example 82 (*See* Table 17).

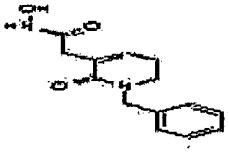
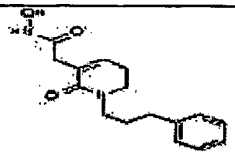
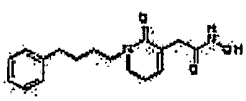
Example 85. Preparation of N-hydroxy-2-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p4)

N-hydroxy-2-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p4) was prepared by the similar procedure described in above Example 82 (*See* Table 17).

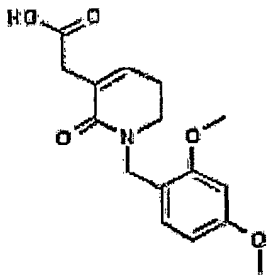
Example 86. Preparation of N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p5)

N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p5) was prepared by the similar procedure described in above Example 82 (*See* Table 17).

[Table 17]

Example	Chemical structure	NMR spectrum data
83		7.34-7.22 (m, 5H), 6.58 (t,J=4.5Hz,1H) 4.60 (s, 2H) 3.39-3.30(m,3H) 3.20 (s,2H) 2.39-2.30 (m,2H)
84		8.21 (d, J=8.7Hz, 1H), 7.44 (d, J=8.7Hz, 2H) 6.63 (t, J=4.3Hz, 1H), 4.75 (s, 2H), 3.41(ab, J=6.5Hz, 4H), 2.43(ab, J=6.2Hz, 2H)
85		7.22 (d, J=6.5Hz, 2H) 7.14(s, 3H) 6.51(br t, 1H) 3.43-3.32 (m,5H) 3.11(s, 1H) 2.59(s,2H) 2.29(s,2H) 1.84(s,2H)
86		7.28-7.13 (m,5H), 6.54(br t, 1H), 3.44-3.31 (m,5H), 3.14(s,1H) 2.62(t,J=7.1Hz,2H), 2.34(s,2H), 1.58(t, J=3.4Hz, 4H)

Example 87. Preparation of [1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid (q1)



[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid methyl ester (o) prepared by the Step 2 of Example 26 dissolved in TFA was reacted with LiOH to give [1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid (q1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ7.18 (d, J=8.7Hz, 1H), 6.54 (t, J=4.3Hz, 1H), 6.45 (d, J=6.6Hz, 2H), 4.60 (s,2H), 3.79(s, 6H) 3.39(t, J=7.3Hz, 2H), 3.34(s, 2H), 2.32(ab, J=11.7Hz, 3.6Hz, 2H)

Example 88. Preparation of (1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q2)

(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q2) was prepared by the similar procedure described in above Example 87 (*See* Table 18).

Example 89. Preparation of (2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q3)

(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q3) was prepared by the similar procedure described in above Example 87 (*See* Table 18).

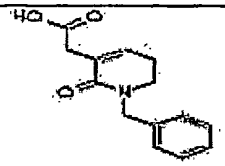
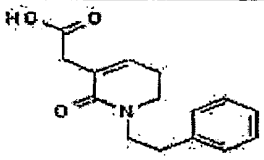
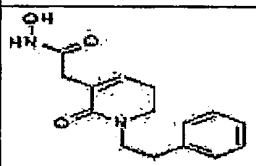
Example 90. Preparation of [2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q4)

[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q4) was prepared by the similar procedure described in above Example 87 (*See* Table 18).

Example 91. Preparation of [2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q5)

[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q5) was prepared by the similar procedure described in above Example 87 (*See* Table 18).

[Table 18]

Example	Chemical structure	NMR spectrum data
88		7.29-7.18 (m 5H) 6.50 (t, J=4.5Hz, 1H), 4.58 (s, 2H), 3.31 (d J=7.2Hz 4H), 2.29 (ab, J=11.0Hz, 3.5Hz, 2H)
89		7.31-7.18 (m,5H), 6.53 (t, J=4.5Hz, 1H), 3.67 (t, J=7.2Hz, 2H), 3.30 (s, 2H), 3.23(t,J=7.2Hz, 2H) 2.90 (t, J=7.2Hz) 2.23 (ab, J=11.7Hz,3.6Hz, 2H)
90		7.32-7.12 (m,5H) 6.47(br t, 1H) 3.56(t, J=10.8Hz, 2H), 3.11 (s,4H) 2.78(d, J=6.0Hz, 2H) 2.14(d, J=10.8Hz, 2H)
91		7.29-7.14 (m,5H), 6.55(t, J=4.2Hz, 1H), 3.46(t, J=6.7Hz, 2H), 3.38(t, J=7.3Hz, 2H), 3.31 (s, 2H) 2.64(t, J=7.1Hz, 2H) 2.37(ab, J=6.3Hz, 2H) 1.67-1.58(m,4H)

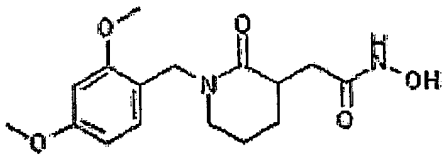
Example 92. Preparation of 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-N-hydroxy-acetamide (s1)

Step 1. Preparation of [1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-acetic acid methyl ester (r)

26mg of [1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid methyl ester(o) (0.08mM) was dissolved in methanol solution under Ar atmosphere. 1.7mg of 10% Pd-C was added thereto and the mixture was hydrogenated under a hydrogen balloon. The reaction mixture was stirred for 5 hrs at room temperature, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography to give 25mg of [1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-acetic acid methyl ester (r) (yield : 99%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J= 8.4 Hz, 2H), 6.41 (dd, J= 8.4 Hz, 2H), 6.41 (s, 1H), 4.51 (dd, J=32.7, 14.9 Hz, 2H), 3.76 (s, 6H), 3.66 (s, 3H), 3.22 (dd, J= 7.5, 4.6Hz, 2H), 2.90 (dd, J=15.9, 5.1 Hz, 1H), 2.76 (m, 1H), 2.52 (dd, J=16.2, 7.5Hz, 2H), 1.98-1.55 (m, 4H)

Step 2. Preparation of 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-N-hydroxy-acetamide (s1)



2-[1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-acetic acid methyl ester (r) prepared by the Step 1 was reacted with amine salt to give [1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-N-hydroxy-acetamide (s1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.15(d, J=9.0Hz,1H), 6.46(t, J=4.65,2H), 4.56 (q, J=7.2Hz, 23.7Hz, 2H), 3.79(s, 6H), 3.31-3.19(m, 2H), 2.86-2.69(m, 2H), 2.41(d, J=14.1Hz, 1H), 1.89-1.79 (m, 2H)

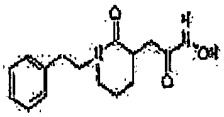
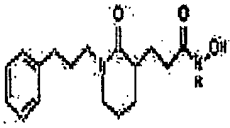
Example 93. Preparation of (2-oxo-1-phenethyl-piperidine-3-yl)-N-hydroxy-acetamide (s2)

(2-oxo-1-phenethyl-piperidine-3-yl)-acetic acid (s2) was prepared by the similar procedure described in above Example 92 (*See* Table 19).

Example 94. Preparation of [2-oxo-1-(3-phenyl-propyl)-piperidine-3-yl]-N-hydroxy-acetamide (s3)

[2-oxo-1-(3-phenyl-propyl)-piperidine-3-yl]-acetic acid (s3) was prepared by the similar procedure described in above Example 92 (*See* Table 19).

[Table 19]

Example	Chemical structure	NMR spectrum data
93		7.315-7.169(m,5H), 3.60(t,J=7.35,1H), 3.15(dd,J=4.8,11.1,1H), 2.917-2.856(m,1H), 2.728-2.659(m,1H), 1.698-1.426(m,4H), 1.23(d,J=7.05,5H)
94		7.29-7.12(m,5H) 3.47-3.35(m,2H) 3.29-3.23(m,2H)2.63-2.45(m,4H) 2.03-1.80(m,4H) 1.59-1.47(m,2H), 1.33-1.19(m,3H)

Example 95. Preparation of 4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-butylamide (v1)

Step 1. Preparation of 5-[(4-methoxy-benzyl)-but-3-enyl-carbamoyl]-hex-5-enoic acid methyl ester (t)

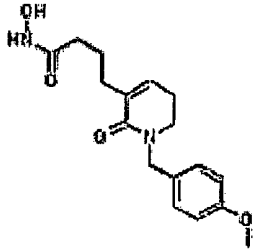
2-Methylene-pentane dionate-5-methyl ester, EDC and DMAP were added to reaction solution dissolving the but-3-enyl-(2,4-dimethoxybenzyl)amine (b) prepared by above Step 1 of Example 1 in methylene chloride solution and the mixture was stirred for 5 hrs at room temperature to give 5-[(4-methoxy-benzyl)-but-3-enyl-carbamoyl]-hex-5-enoic acid methyl ester (t).

Step 2. Preparation of 4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-butyric acid methyl ester (u)

5-[(4-methoxy-benzyl)-but-3-enyl-carbamoyl]-hex-5-enoic acid methyl ester (t) prepared by above Step 1 was added to the catalyst solution containing Grubb's (I) catalysis such as ruthenium dissolved in organic solvent such as CH_2Cl_2 to give 4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-butyric acid methyl ester (u).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.19(d, J=8.4Hz, 2H), 6.83(d, J=8.4Hz, 2H), 6.25 (t, J=4.2Hz, 1H), 4.54 (s, 2H), 3.77 (s, 3H), 3.65 (s, 3H), 3.25(t, J=6.9Hz, 2H) 2.33 (t, J=7.3Hz, 4H), 2.24 (q, J=4.5Hz, 2H), 1.80 (t, J=7.2Hz, 2H) 1.56(s, 2H)

Step 3. Preparation of 4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-butylamide (v1)



4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-butyric acid methyl ester (u) prepared by Step 2 dissolved in alcohol solvent was reacted with amine salt to give 4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-butylamide (v1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.19-7.15 (m,2H), 6.83 (d,*J*=7.8Hz, 2H), 6.28 (br t, 1H), 4.53 (s, 2H), 3.76 (s, 3H), 3.25(dt, *J*A=7.5Hz, *J*B=1.8Hz, 2H), 2.38-2.23 (m, 6H), 1.85-1.76 (m, 2H)

Example 96. Preparation of 4-(1-phenethyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-butylamide (v2)

4-(1-phenethyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-butylamide (v2) was prepared by the similar procedure described in above Example 95 (*See* Table 20).

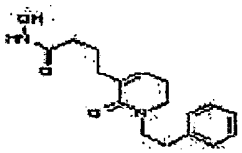
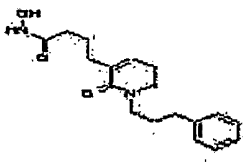
Example 97. Preparation of N-hydroxy-4-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide (v3)

N-hydroxy-4-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide (v3) was prepared by the similar procedure described in above Example 95 (*See* Table 20).

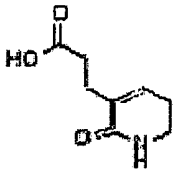
Example 98. Preparation of N-hydroxy-4-[2-oxo-1-(3-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide (v4)

N-hydroxy-4-[2-oxo-1-(3-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide (v4) was prepared by the similar procedure described in above Example 95 (*See* Table 20).

[Table 20]

Example	Chemical structure	NMR spectrum data
96		7.29-7.13(m,5H), 6.24(br t,1H), 3.56 (t,J=7.56Hz 2H), 3.31-3.29 (m, 1H), 3.16 (t, J=6.9Hz, 2H), 2.80(t, J=7.2Hz, 2H), 2.14-2.03 (m, 5H), 1.66-1.61 (m, 2H)
97		7.29-7.17(m,5H), 6.32(br t,1H), 3.46 (t,J=7.3Hz 2H), 3.35 (t, J=5.9Hz, 2H), 2.63 (t, J=7.6Hz, 2H), 2.37-2.28(m, 5H), 1.99-1.73 (m, 5H)
98		7.29-7.15(m,5H), 6.31(br t,1H), 3.45 (t,J=6.5Hz 2H), 3.32 (t, J=7.1Hz, 2H), 2.64 (t, J=7.0Hz, 2H), 2.27(d, J=7.2Hz, 6H), 1.60 (s, 6H)

Example 99. Preparation of 3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (g)

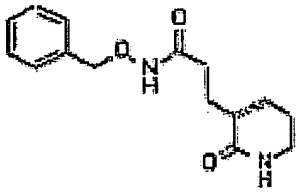


50mg of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (0.157 mM) was dissolved in 1 ml of trifluoroacetic acid solution. Then 0.074ml of triethyl silane (0.465 mmol) was added thereto and the mixture was heated for 20 min at 80°C. The solvent was removed *in vacuo* and the remaining residue was recrystalized with mixture solution of methanol and ethylacetate to give 13mg of 3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (g) (yield : 50%).

^{1}H-NMR (300 MHz, CD_3OD), δ 6.51(m, 1H), 3.31(m, 2H), 2.50(m, 4H), 2.32(m, 2H)

^{13}C-NMR (75 MHz, CD_3OD), δ 176.7, 168.6, 138.4, 134.5, 40.3, 34.1, 27.1, 25.0

Example 100. Preparation of N-Benzyloxy-3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (h)



29mg of 3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (g) was dissolved in 0.5 ml of DMF solution (0.171mM). 30mg of $BnONH_2 \cdot HCl$ (0.188 mM), 0.033ml of diisopropyl methylamine (0.189 mM), 43mg of EDC (0.224 mM) and 5mg of DMAP (0.041 mM) were added thereto and the mixture was stirred for overnight at room temperature. The mixture was diluted with 7 ml of ethyl acetate and washed with 5% HCl (1 ml) and 1ml of sat. $NaHCO_3$ solution. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:20) solvent mixture as an eluant to give 126 mg of the title compound (h) (yield : 55%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.28(s, br, 1H), 7.35(m, 5H), 6.45(s, br, 1H), 5.70(s, br, 1H), 4.87(s, 2H), 3.47(s, br, 2H), 2.53(m, 2H), 2.27(m, 4H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.1, 166.9, 137.8, 135.6, 133.0, 129.1, 128.5, 78.0, 39.7, 32.8, 26.9, 24.1

Example 101. Preparation of 3-(1-Allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide (j1)

Step 1. Preparation of 3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (f)

310mg of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (d) (0.93 mM) was dissolved in 3 ml of trifluoroacetic acid solution. Then 0.222ml of triethyl silane (1.395 mmol) was added thereto and the mixture was heated for 20 min at 80°C. The solvent was removed *in vacuo* and the remaining residue was diluted in 20ml of chloroform. The organic layer was washed with 5ml of sat. $NaHCO_3$ solution and 5ml of sat. NaCl solution. Then the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with EtOAc solvent as an eluant to give 126mg of the title compound (f) (yield : 55%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ6.64(s, br, 1H), 6.35(t, *J*=3.0 Hz, 1H), 3.59(s, 3H), 3.31(m, 2H), 2.48(m, 4H), 2.26(m, 2H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ173.4, 166.8, 136.1, 133.5, 51.4, 39.5, 33.1, 26.0, 24.0

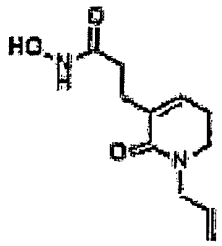
Step 2. Preparation of 3-(1-allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (i1)

0,220ml of NaHMDS solution (1.0 M in THF, 0.22 mM) was added to 0.5ml of the THF solution containing 40mg of 3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (0.218 mM) prepared by the Step 1 in a dropwise manner at -79 °C and stirred at -79 °C for 30 mins. After 0.028ml of allyl bromide (0.327 mM) was added to the reaction mixture, the mixture was stirred at 0 °C for 3 hrs. The reaction mixture was quenched by 2ml of sat. NH_4Cl solution and then the organic layer was extracted with 7ml of ethyl acetate. The combined organic layer was washed with 2ml of sat. NH_4Cl solution and 2ml of sat. NaCl solution. Then the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with EtOAc/hexane (1:2) solvent mixture as an eluant to give 36mg of the title compound (i1) (yield : 74%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.28(m, 1H), 5.74(m, 1H), 5.14(m, 2H), 3.99(d, *J*=5.7 Hz 2H), 3.61(s, 3H), 3.27(t, *J*=6.9 Hz, 2H), 2.51(m, 4H), 2.27(m, 2H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.6, 164.6, 134.3, 134.1, 133.3, 117.1, 51.4, 49.0, 44.6, 33.3, 26.6, 23.8

Step 3. Preparation of 3-(1-allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide (j1)



24mg of 3-(1-allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (i1) prepared from the above Step 2 was dissolved in methanol solution (0.11 mM) and then 0.122ml of 1.7M NH_2OK suspension solution (0.207 mM) was added thereto

at 0°C and stirred for 3 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10 ml of ethyl acetate solution, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:10) solvent mixture as an eluant to give 11 mg of the title compound (j1) (yield : 48%).

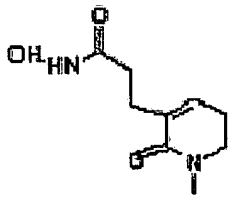
^{1}H-NMR (300 MHz, $CDCl_3$) : δ6.39(br t, 1H), 5.78-5.67(m, 1H), 5.17(d, *J*=5.4 Hz, 1H), 5.12(s, 1H), 3.98(d, *J*=5.4 Hz, 2H), 3.30(t, *J*=7.0 Hz, 2H), 2.54-2.28 (m, 6H)

Example 102. Preparation of N-hydroxy-3-(1-methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (j2)

Step 1. Preparation of 3-(1-methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (i2)

0.22ml of 1.0M NaHMDS solution in THF (0.22 mM) was added to 0.5ml of THF solution containing 80mg 3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (f) prepared from the step 1 in Example 3 (0.44 mM) in a dropwise manner at -79 °C and then stirred for 30 min. After 0.48ml of methyl bromide (0.48 mM) was added to the reaction mixture, the solution was stirred at 0 °C for 3 hrs. The reaction mixture was quenched by 2ml of sat. NH_4Cl solution and then the organic layer was extracted with ethyl acetate (7 ml). The combined organic layer was washed with 2ml of sat. NH_4Cl solution (2 ml) and 2ml of sat. NaCl solution subsequently. Then the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with EtOAc solvent as an eluant to give 62mg of the title compound (i2) (yield : 72%).

Step 2. Preparation of N-hydroxy-3-(1-methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (j2)



50mg of 3-(1-methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester prepared from the above Step 1 was dissolved in methanol (0.25 mM)

and then 0.122ml of 1.7M NH_2OK suspension solution in methanol (0.207 mM) was added thereto at 0°C and the resulting mixture was stirred for 3 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10 ml of ethyl acetate, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:20) solvent mixture as an eluant to give 19 mg of the title compound (j2) (yield : 35%).

^{1}H-NMR (300 MHz, CD_3OD) δ 6.15(t, J=4.3 Hz, 1H), 3.41(t, J=7.2 Hz, 2H), 2.97(s, 3H), 2.51(t, J=7.5 Hz, 2H), 2.35(m, 2H), 2.22(t, J=7.5 Hz, 2H)

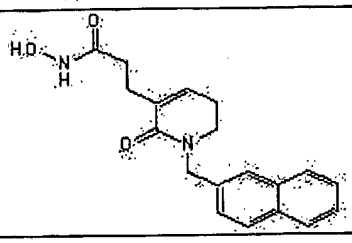
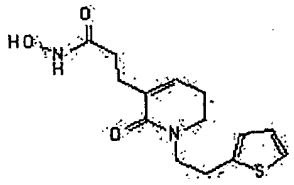
Example 103. Preparation of N-hydroxy-3-(1-(naphthalene-2-yl-methyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide

70mg of 3-[1-(Naphthyl-2-yl)methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester was dissolved in methanol solution (0.22 mM) and then 0.64ml of 1.7M NH_2OK suspension in methanol (1.08 mM) was added thereto at 0°C and the resulting mixture was stirred for 5 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid and concentrated *in vacuo*. The resulting solid was filtered with 10% methanol/chloroform solvent mixture and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:9) solvent mixture as an eluant to give 61 mg of the title compound (*See* Table 21) (yield : 95%).

Example 104. Preparation of N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide

60mg of 3-[2-oxo-1-(2-thiophen-2-yl)ethyl-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester was dissolved in methanol to be 0.20 mM solution and then 0.6ml of 1.7M NH_2OK suspension solution in methanol (1.02 mM) was added thereto at 0°C and the resulting mixture was stirred for 5 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid and concentrated *in vacuo*. The resulting solid was filtered with 10% methanol/chloroform solvent mixture and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:9) solvent mixture as an eluant to give 44 mg of the title compound (*See* Table 21) (yield : 73%).

[Table 21]

Example	Chemical structure	NMR spectrum data
103		8.07-7.99 (m, 1H), 7.83-7.74 (m, 2H), 7.50-7.29 (m, 4H), 6.32 (br t, 1H), 5.01 (s, 2H), 3.44(s, 2H), 3.15 (q, J=6.9 Hz, 2H), 2.71-2.54 (m,2H), 2.42 (s, 2H), 2.09 (s, 2H)
104		7.11 (d, J=4.8 Hz, 1H), 6.89 (t, J=3.9 Hz, 1H), 6.82 (s, 1H), 6.35 (br t, 1H), 3.64-3.59 (m, 2H), 3.22 (t, J=3.22 Hz, 2H), 3.09-3.04 (m, 2H), 2.54-2.50 (m, 2H), 2.35 (s, 2H), 2.20(s, 2H)

Example 105. Preparation of 3-(1-Benzyl-2-oxo-2,5,6,7-tetrahydro-1H-azepin-3-yl)-N-hydroxy-propionamide (e1)

Step 1. Preparation of Benzyl-pent-4-enyl-amine (b)

0.397ml of 5-Bromo-1-pentene (3.35 mmol) and 0.67 ml of diisopropyl ethylamine (3.96 mmol) were added to the reaction solution containing 0.74ml of benzylamine(a) (4.93 mmol) dissolved in acetonitrile with stirring and the mixture was stirred at room temperature for overnight. The reaction mixture was washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with EtOAc solvent as an eluant to give 236mg of the pure title compound (b) (yield: 44%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35-7.24(m,5H), 5.92-5.78 (m,1H), 5.09-4.98 (m,2H), 3.80 (s, 2H), 2.67(t, *J*=7.5Hz,), 2.14 (q, *J*=7.5Hz,2H), 1.69-1.59 (m, 2H), 1.41 (br, 1H)

Step 2. Preparation of Preparation of 4-(Benzyl-pent-4-enyl-carbamoyl)-pent-4-enoic acid methyl ester (c)

320 mg of 2-methylene-pentane dionate-5-methyl ester (2.02 mmol), 340 mg of EDC (2.02 mmol) and 50mg of DMAP (0.405 mmol) were added to 0.5 M of reaction solution dissolving the compound (b) prepared by above step 1 in methylene chloride and the mixture was stirred for 5 hrs at room temperature. The resulting

mixture was diluted with ethyl acetate, and washed with 5% HCl solution (10 ml) and 10 ml of saturated $NaHCO_3$ solution to separate into an organic layer and water layer. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:2) as an eluant to give 150mg of 4-[but-3-enyl-(2,4-dimethoxybenzyl)-carbamoyl]-pent-4-enoic acid methyl ester (c) (yield : 35%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31-7.14 (m,5H), 5.81-5.64 (m,1H) 5.12 (s,1H), 5.04-4.97 (m,3H), 3.65 (s ,2H), 3.56-3.46 (m,3H), 3.42-3.36 (m,1H), 3.33-3.31(m,1H), 2.85(d,J=3Hz, 2H), 2.65-2.45 (m, 4H), 2.07-2.01(m, 2H), 1.69-1.59(m, 2H)

Step 3. 3-(1-Benzyl-2-oxo-2,5,6,7-tetrahydro-1H-azepin-3-yl)-propionic acid methyl ester (d)

150 mg of the compound (c) (0.476 mmol) prepared by the above Step 2 was added to the catalyst solution containing 40 mg of ruthenium (0.047 mmol) dissolved in CH_2Cl_2. Then the mixture was stirred for 24 hrs at room temperature, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with methanol/chloroform (1:10) solvent mixture as an eluant to give 108 mg of the title compound (d) (yield : 79%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.28-7.26 (m, 5H), 5.99-5.94 (m, 1H), 4.63(s,2H), 3.60 (S, 2H), 3.21(t, J=6Hz 2H), 2.65(t, J=7.2Hz,2H), 2.48(t, J=6.9Hz,2H), 2.08-2.01 (m, 2H), 1.67-1.57(m, 2H)

Step 4. Preparation of 3-(1-Benzyl-2-oxo-2,5,6,7-tetrahydro-1H-azepin-3-yl)-N-hydroxy-propionamide (e1)

108 mg of compound (d) prepared by the above Step 3 was dissolved in methanol solution (0.376 mmol) and then 1,7 M methanolic suspension solution containing NH_2OK (1.315 ml, 2.63 mmol) was added thereto at 0°C and the resulting mixture was stirred for 3 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10 ml of ethyl acetate solution, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:10) solvent mixture as an eluant to give 46 mg of the title compound (e1) (yield: 43%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ7.28-7.24 (m,5H), 6.20-6.02 (m,2H), 4.65 (s,2H), 3.26(d,J=3Hz,2H), 2.66-2.52 (m, 4H), 2.08-2.05(m,2H), 1.65-1.64(m,2H)

Example 106. Preparation of N-Hydroxy-3-[2-oxo-1-(3-phenyl-ethyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide (2e)

N-Hydroxy-3-[2-oxo-1-(4-phenylethyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide (2e) was prepared by the similar procedure described in above Example 105 (*See* Table 22).

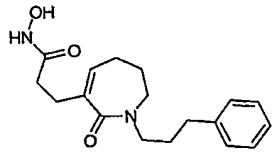
Example 107. Preparation of N-Hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide (3e)

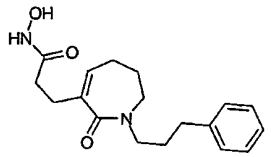
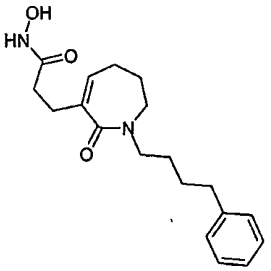
N-Hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide (3e) was prepared by the similar procedure described in above Example 105 (*See* Table 22).

Example 108. Preparation of N-Hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide (4e)

N-Hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide (4e) was prepared by the similar procedure described in above Example 105 (*See* Table 22).

[Table 22]

Example	Chemical Structure	NMR Spectral data
106		7.3-7.20 (m,5H), 6.05 (t,J=6Hz,1H), 3.70 (t, J=6Hz, 2H), 3.17,(t,J=6Hz,2H), 2.89(t,J=6Hz,2H), 2.58-2.35(m,4H), 2.00 (t,J=6Hz,2H), 1.74(t,J=6Hz,2H)

107		7.31-7.12 (m, 5H), 6.11-6.05 (m,1H), 3.50 (br,2H) 3.25(br,2H), 2.76-2.47 (m, 6H), 2.17-2.09 (br,2H), 1.91-1.88 (br,2H)
108		7.27-7.13 (m,5H), 6.07-6.05 (m,1H), 3.44(br, 2H), 3.22(br, 2H), 2.62-2.43(m,6H), 2.09-2.07(br,2H), 1.84-1.82(br, 2H), 1.65-1.55(br,4H)

Experimental Example 1. Effect of the compound of the present invention on HDAC

To test the inhibiting effect of the compounds prepared from above Examples 1 to 108 on histone deacetylase (HDAC), HDAC Flurescent Activity Assay/Drug Discovery Kit (Biomol, USA) was used with nuclear extracts of HeLa cell as a HDAC source. Fluorogenic Histone Deacetylase Lysyl Substrate was used as substrate for HDAC and the test is based on the fact that the removal of acetyl group by HDAC activity causes the substrate to occur emmition wavelength in the ranging from 360 nm to 460 nm.

Various concentrations of the compounds of the present invention ranging from 0.01 to 10 μM were reacted with HDAC enzyme at 25°C for 20 minutes and equal volume of developer was added thereto. The fluorescence signal was detected at the wavelength in the range 350 to 460nm using by fluorescence spectrometer. IC_{50} value is defined as the concentration of the sample required to reduce the maximum fluorescence to a half and the result was shown in Table 2.

As shown in Table 2, it was confirmed that compounds of the present invention showed potent inhibiting effect on the activity of HDAC enzyme.

Experimental Example 2. Effect of the compound of the present invention on the tumor cell growth

PC-3 cells (ATCC, US), human prostatic carcinoma cell line, were cultured in RMPI 1640 supplemented with 10% fetal bovine serum.

Appropriate concentrations of cells ($5x10^4$ cells/ml) cultured in RMPI 1640 supplemented with 5% fetal bovine serum were poured into 96-well plate and incubated

at 37°C in 5% CO_2 condition. The day after the incubation, PC-3 cells were fixed on Time zero (T_0) plate by adding 50 μl/well of 50% trichloroacetic acid and the cell concentration was set to zero point by fixing the cells. In the cells treated with test samples, 50% TCA was added to each wells in 50ul/well after 48 hrs to fix the cells. The final concentration of adding test compounds were 0.01, 0.03, 0.1, 0.3, 1 μg/ml respectively. Then, each fixed plate was washed, dried and 100 μl/well of 0.4% reaction solution containing sulforhodamine B (SRB) reagent dissolved in 0.1% acetic acid was added thereto to stain the cells. 30 minutes later, the cell was washed with 0.1% acetic acid, dried at room temperature, and 10 mM of TRIS base (pH 10.5) was added thereto to dissolve the staining agent. Finally, the absorbance detected at 540 nm was measured and the value was conversed into percentage comparing with that of control group. IC_{50} ($\mu g/m\ell$), the concentration of the group required to inhibit the cancer cell growth by 50%, was calculated from the data (AA : IC_{50}'s < 1, A : IC_{50}'s < 5, B: IC_{50}'s < 10 and C : IC_{50}'s > 10). Also, the inhibiting activity of cell growth was expressed as various symbols in accordance with the potency of examples e.g., AA: closely equivalent (1~2 times), A: slightly weaker (3~5 times), B: weaker (5~10 times), C: very weaker (more than 10 times) than that of adriamycin used as a positive control group. The result was shown in Table 23.

As shown in Table 23, it was confirmed that compounds of the present invention inhibited HDAC directly and showed potent inhibiting effect on the activity of cancer cell growth, especially, PC-3 cancer cell.

[Table 23]

Example	HDAC inhibition	Cell growth inhibition	Example	HDAC inhibition	Cell growth inhibition
1	AA	A	31	A	A
2	AA		32	A	A
3	AA	AA	33	A	A
4	AAA	A	34		A
5	C		35		A
6	AA	B	36		A
7	AA	A	37		A
8	AA	A	38		A
9	C	A	39		A
10		AA	40		A
11		AA	41		B
12	AA	AA	42		AA
13	AA	A	43		A
14	A	B	44		B
15			45		B
16	C	C	46		B
17	C	C	47		
18		B	48		
19		B	49	AA	A
20	C	C	50	A	AA
21	C	C	51	A	C
22	C	C	52		
23	C	C	53		AA
24	C	C	54	C	A
25	C	C	55	AA	AA
26	C	C	56	AA	AAA
27	C	C	57	AA	AA
28		A	58	AA	B
29		A	59	AA	B
30		A	60	AA	B

Example	HDAC inhibition	Cell growth inhibition	Example	HDAC inhibition	Cell growth inhibition
61	AA	AA	85	C	
62	AA	AA	86	C	C
63	C	C	87	C	
64	C	C	88	C	
65	C	C	89	C	
66	C	C	90	C	
67	C	C	91	C	
68	C	C	92	C	C
69	C	C	93	C	
70	C		94	C	
71	C		95	C	C
72	C		96	C	
73	C	C	97	A	
74	AA	C	98	A	
75	AA	B	99	C	
76	A	C	100	C	
77	AA	A	101	C	C
78	C		102	C	C
79	C		103	C	B
80	C		104	C	B
81	A	C	105	C	C
82	C	C	106	C	C
83	C	C	107	C	C
84	C		108	C	C

Experimental Example 3. Toxicity test

Methods

The acute toxicity tests on ICR mice (mean body weight 25±5g) and Sprague-Dawley rats (235±10g, Jung-Ang Lab Animal Inc.) were performed using the

compounds of example 80. Four group consisting of 10 mice or rats was administrated orally with 4mg/kg, 40mg/kg, 400mg/kg and 4,000mg/kg of test sample or solvents (0.2 ml, i.p.) respectively and observed for 2 weeks.

Results

There were no treatment-related effects on mortality, clinical signs, body weight changes and gross findings in any group or either gender. These results suggested that the extract prepared in the present invention were potent and safe.

Hereinafter, the formulating methods and kinds of excipients will be described, but the present invention is not limited to them. The representative preparation examples were described as follows.

Preparation of powder

the compounds of example 80	50mg
Lactose	100mg
Talc	10mg

Powder preparation was prepared by mixing above components and filling sealed package.

Preparation of tablet

the compounds of example 80	50mg
Corn Starch	100mg
Lactose	100mg
Magnesium Stearate	2mg

Tablet preparation was prepared by mixing above components and entabletting.

Preparation of capsule

the compounds of example 80	50mg
Corn starch	100mg
Lactose	100mg
Magnesium Stearate	2mg

Tablet preparation was prepared by mixing above components and filling gelatin capsule by conventional gelatin preparation method.

Preparation of injection

the compounds of example 80	50mg

Distilled water for injection	optimum amount
PH controller	optimum amount

Injection preparation was prepared by dissolving active component, controlling pH to about 7.5 and then filling all the components in 2 ㎖ ample and sterilizing by conventional injection preparation method.

Preparation of liquid

the compounds of example 80	0.1~80g
Sugar	5~10g
Citric acid	0.05~0.3%
Caramel	0.005~0.02%
Vitamin C	0.1~1%
Distilled water	79~94%
CO_2 gas	0.5~0.82%

Liquid preparation was prepared by dissolving active component, filling all the components and sterilizing by conventional liquid preparation method.

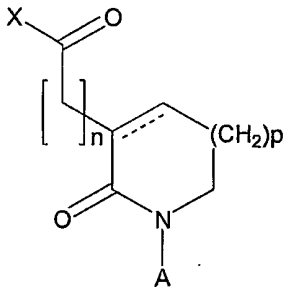
The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the present invention, and all such modifications as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

INDUSTRIAL APPLICABILITY

As described in the present invention, the 2-oxo-cyclic compound of the present invention have potent anti-cancer activity, therefore, it can be used as the therapeutics for treating and preventing the cancer disease comprising lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer or cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphonas, cancer of the bladder, cancer of the kidney or ureter, or neoplasms of the central nervous system.

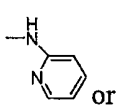
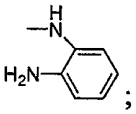
What is claimed is;

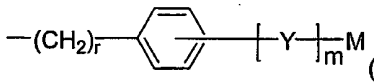
1. A use of a compound represented by the following general formula (I), and the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(I)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

A is an hydrogen, A1 group or  (A2),

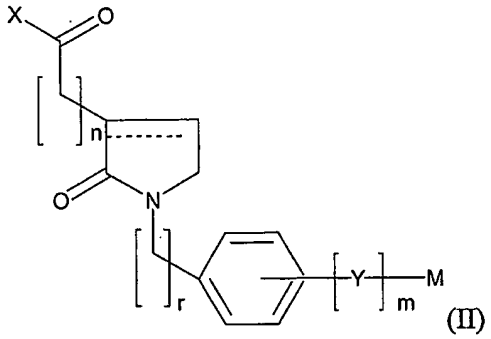
A1 is a lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C5 carbon atoms, a heterocyclic group or aromatic aryl group, preferably, the group selected from thiopenyl group, naphtyl group, pyrrolyl group, furyl group and biphenyl group, wherein the Y in A2 substituted is a lower alkyl group, lower alkoxy group, nitro, halogen, amine, acetamide, carbonamide or sulfonamide group, M is a lower alkyl group or phenyl group substituted with R', of which R' is a hydrogen, lower alkyl or lower alkoxy group, m and r is independently an integer of 1 to 5 respectively;

p is an integer of 0, 1 or 2;

n is an integer of 1 to 5;

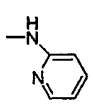
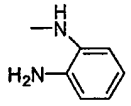
dotted line (⁼) means single bond or double bond.

2. A use of a compound represented by the following general formula (II), and the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(II)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

Y is a lower alkyl group, lower alkoxy group, nitro, halogen, amine, acetamide, carbonamide or sulfonamide group;

M is a lower alkyl group or phenyl group substituted with R', of which R' is a hydrogen, lower alkyl or lower alkoxy group;

m and r is independently an integer of 1 to 5 respectively;

n is an integer of 1 to 5;

dotted line (⁼) means single bond or double bond.

3. The use according to claim 2, wherein said compound is one selected from the group consisting of;

3-[1-(2,4-Dimethoxybenzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxypropionamide,

3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-propionamide,

N-hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(2-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(3-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(4-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(2-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(3-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-

propionamide,

3-[1-(4-bromo-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide,

3-[1-(4-chloro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide,

3-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide,

N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid,

3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid,

N-{4-[3-(2-hydroxycarbamoyl-ethyl)-2-oxo-2,5-dihydro-pyrrole-1-yl-methyl]-phenyl}-benzamide,

N-hydroxy-3-{2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

2-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-acetamide,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)- acetamide,

N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]- acetamide,

2-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide,

2-(1-benzyl-2-oxo-pyrrolidin-3-yl)-N-hydroxy-acetamide,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-pyrrolidin-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-(2-oxo-1-phenethyl-pyrrolidin-3-yl)- acetamide,

3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

3-{1-[2-(3-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

3-{1-[2-(4-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

N-hydroxy-3-{1-[2-(2-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(3-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(4-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

3-{1-[2-(2-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

3-{1-[2-(4-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-

propionamide,

N-hydroxy-3-{1-[2-(2-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(3-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(4-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-[2-oxo-1-(2-*p*-tolyl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-[2-oxo-1-(3-*o*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(3-m-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-{1-[3-(4-isopropyl-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-{1-[3-(4-bromo-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

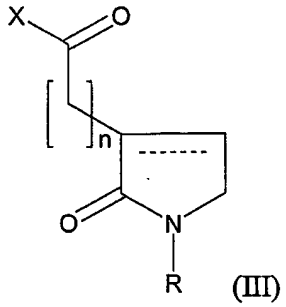
3-{1-[3-(4-chloro-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-{1-[3-(2-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

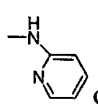
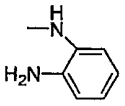
N-hydroxy-3-{1-[3-(3-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide.

4. A use of a compound represented by the following general formula (III), and the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(III)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

R is a lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C5 carbon atoms, a heterocyclic group or aromatic aryl group;

n is an integer of 1 to 5;

dotted line (---) means single bond or double bond.

5. The use according to claim 4, wherein said R is the group selected from thiopenyl group, naphtyl group, pyrrolyl group, furyl group and biphenyl group.

6. The use according to claim 5, wherein said compound is one selected from the group consisting of;

N-hydroxy-3-(1-naphthalene-2-ylmethyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide,

N-hydroxy-3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide,

3-(1-allyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-[1-(2-naphthalene-1-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

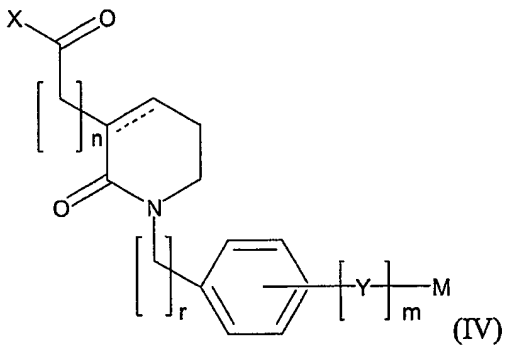
N-hydroxy-3-[1-(2-naphthalene-2-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-[1-(3-biphenyl-4-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

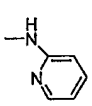
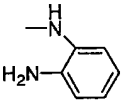
N-hydroxy-3-[1-(3-naphthalene-2-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide.

7. A use of a compound represented by the following general formula (IV), and the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(IV)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

Y is a lower alkyl group, lower alkoxy group, nitro, halogen, amine, acetamide, carbonamide or sulfonamide group;

M is a lower alkyl group or phenyl group substituted with R', of which R' is a hydrogen, lower alkyl or lower alkoxy group;

m and r is independently an integer of 1 to 5 respectively;

n is an integer of 1 to 5;

dotted line (⁼) means single bond or double bond.

8. The use according to claim 7, wherein said compound is one selected from the group consisting of;

3-[1-(2,4-Dimethoxybenzyl)-2-oxo-1,2,5,6-tetragydropyridine-3-yl]N-hydroxypropionamide,

N-hydroxy-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy propionamide,

N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

N-hydroxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-pyridin-2-yl-propionamide,

N-(2-amino-phenyl)-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-benzyloxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide,

N-4-[5-(2-hydroxycarbamoyl-ethyl)-6-oxo-3,6-dihydro-2-pyridin-1-yl-methyl]-phenyl-benzamide,

N-hydroxy-3-[1-(4-dimethylsulfonylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

N-hydroxy-3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid,

3-[1-(4-benzoylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid,

3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid,

N-hydroxy-3-(2-oxo-1-phenethyl-piperidine-3-yl)-propionamide,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide,

2-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide,

N-hydroxy-2-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide,

N-hydroxy-2-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide,

[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid,

(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-N-hydroxy-acetamide,

(2-oxo-1-phenethyl-piperidine-3-yl)-acetic acid,

[2-oxo-1-(3-phenyl-propyl)-piperidine-3-yl]-acetic acid,

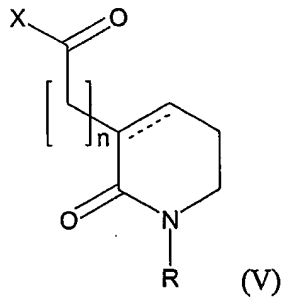
4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-butylamide,

4-(1-phenethyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-butylamide,

N-hydroxy-4-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide,

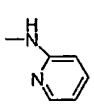
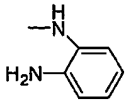
N-hydroxy-4-[2-oxo-1-(3-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide.

9. A use of a compound represented by the following general formula (V), and the pharmaceutically acceptable salt or the isomer thereof for the preparation of pharmaceutical composition to treat and prevent cancer diseases:



(V)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

R is a lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C5 carbon atoms, a heterocyclic group or aromatic aryl group, preferably, the group selected from thiopenyl group, naphtyl group, pyrrolyl group, furyl group and biphenyl group;

n is an integer of 1 to 5;

dotted line (⁻⁻) means single bond or double bond.

10. The use according to claim 9, wherein said compound is one selected from the group consisting of;

3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

N-Benzyloxy-3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

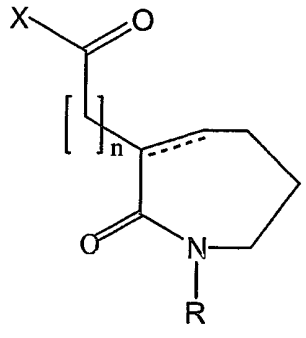
3-(1-Allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-(1-methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-hydroxy-3-(1-(naphthalene-2-yl-methyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

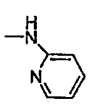
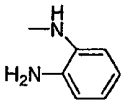
N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide.

11. A novel compound represented by the following general formula (VI), the pharmaceutically acceptable salt or the isomer thereof:



(VI)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

R is independently hydrogen atom, lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C4 carbon atoms substituted with a phenyl group which can be substituted with halogen atom or lower alkyl group;

n is an integer of 1 to 5;

dotted line (⁼) means single bond or double bond.

12. The compound according to claim 11, wherein said compound is one selected from the group consisting of;

N-3-(1-benzyl-2-oxo-2,5,6,7-tetrahydro-1H-azepin-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-[2-oxo-1-(3-phenyl-ethyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(3-phenyl-butyl)-2,5,6,7-tetrahydro-1H-azepin-3-yl]-propionamide.

13. A use of the compound of general formula (VI) as set forth in claim 12 or the pharmaceutically acceptable salt thereof as an active ingredient in amount effective to treat or prevent cancer disease together with pharmaceutically acceptable carriers or diluents.

14. The use according to any one of claims 1 to 11 and 13, wherein said cancer disease comprises lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer or cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphonas, cancer of the bladder, cancer of the kidney or ureter, and neoplasms of the central nervous system.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2004/001764

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 31/4015

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC7 A61K 31/4015

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean patents and applications for inventions since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN(Caslink)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/24797 A1 (MERCK & CO.,INC.) 12 April 2001 See p73, compound 2-4a,b.	1 - 14
A	WO 02/078679 A2 (TOPOTARGET APS) 10 October 2002 See page 21 and claim1.	1 - 14
A	EP 1138680 A1 (PFIZER PRODUCTS INC.) 04 October 2001 See p40, Table 1.	1 - 14
A	WO 97/12902 (CHIROSCIENCE LIMITED) 10 April 1997 See the whole document.	1 - 14

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 SEPTEMBER 2004 (07.09.2004)	07 SEPTEMBER 2004 (07.09.2004)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR2004/001764

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